Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of NICE – Protocol

1. Title of the project

Omalizumab for the treatment of severe persistent allergic asthma. (Review of TA133 and TA201).

2. Name of TAR team and "lead"

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3. Plain English Summary

Asthma is a long-term disorder of the airways which results in ongoing inflammation. This leads to repeated episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. Asthma may be allergic or non-allergic. Allergic asthma is caused by the production of too much immunoglobulin E (IgE) in response to environmental allergens such as house dust mite, pollen, and moulds. Asthma also varies in severity and there is a recognised progression of treatment steps for increasing severity of the disease. Severe persistent allergic asthma is considered to be asthma which is poorly controlled despite the elimination of modifiable factors and the correct use of medication including short-acting relief medication plus high doses of inhaled steroids, and an additional preventer drug. Patients with poorly controlled asthma are at risk of asthma exacerbations which may be serious and require unplanned medical intervention and sometimes hospitalisation, as well as reduced quality of life as a consequence of the day-to-day symptoms. The next step in treatment usually takes the form of the addition of continuous or frequent long-term oral steroids. Oral steroids are associated with a number of serious side

effects which include reduced bone density in adults and growth restriction in children. The purpose of this project is to assess the benefits and safety of omalizumab added to standard therapy for adults, adolescents aged over 12 and children aged between six and 12 who have allergic asthma which is poorly controlled with optimised standard therapy. It will also assess the cost-effectiveness of omalizumab in these patients. Omalizumab is currently recommended by NICE for adults and adolescents but is not recommended for use in children aged under 12 years.

4. Decision problem

Objectives

The aim of the project is to determine the clinical effectiveness, safety and cost-effectiveness of omalizumab, within its licensed indication, in addition to standard therapy compared to standard therapy without omalizumab for the treatment of severe persistent allergic asthma in a) adults and adolescents aged at least 12 years and b) children aged six to 12 years.

Background

There is no single definition for asthma as the type, severity and frequency of symptoms varies. An operational description of asthma is “Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment”.[1]

Distinctions are made between allergic and non-allergic asthma. Allergic asthma results from the over-expression of immunoglobulin E (IgE) in response to environmental allergens such as house dust mite, pollen, and moulds. Distinctions are also made for asthma severity, dependent on the intensity of treatment required to achieve good asthma control. Severe persistent allergic (IgE mediated) asthma can severely limit daily life and can sometimes be fatal.[1]

According to Asthma UK 5.4 million people in the UK are currently receiving treatment for asthma; 1.1 million are children and 4.3 million adults. Asthma UK estimate that between April 2006 and March 2007 there were 67,077 emergency hospital admissions in England, with more than 40% of these (27,970) for children aged 15 years or younger and reported

that in 2009 in the UK there were 1,131 deaths from asthma (12 were children aged 14 years or younger)(www.asthma.org.uk). There are also quality of life issues for patients with asthma, and social and financial implications.[1]

Current treatment strategies

Treatment of asthma to achieve control is based on a stepped approach to therapy; if asthma is not controlled on current treatment, then treatment is stepped up until control is achieved.(1) According to the Global Initiative for Asthma (GINA 2010)[1] and Scottish Intercollegiate Guidelines Network (SIGN) guidelines[2] there are five treatment steps; patients with severe persistent asthma are treated at steps 4 and 5. Treatment at each step is summarised in Table 1.

Step 1	Mild intermittent asthma
	Inhaled short-acting $beta_2$ agonists as required
Step 2	Regular preventer therapy
	Add inhaled steroid 200–800 mcg/day[a]
	400 mcg is an appropriate starting dose for many patients
	Start at the dose of inhaled steroid appropriate to severity of disease
Step 3	Add-on therapy
	Add inhaled LABA
	Assess control of asthma:
	• good response to LABA – continue LABA
	• benefit from LABA but control still inadequate – continue LABA and increase inhaled steroid dose to 800 mcg/day[a]
	• no response to LABA – stop LABA and increase inhaled steroid to 800 mcg/day[a]
	• if control still inadequate, institute trial of other therapies, e.g. leukotriene receptor antagonist or SR theophylline
Step 4	Persistent poor control
	Increase inhaled steroid up to 2000 mcg/day[a]
	Add a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, $beta_2$ agonist tablet
Step 5	Continuous or frequent use of oral steroids
	Use daily steroid tablet in the lowest dose providing adequate control
	Maintain high dose inhaled steroid at 2000 mcg/day[a]
	Consider other treatments to minimize the use of steroid tablets
	Refer patient for specialist care

Table 1: Steps 1 to 5 in treatment of asthma to achieve control.[3]

At step 4, a small proportion of patients have inadequately controlled asthma despite treatment with a combination of short-acting B_2 agonists (SABAs), inhaled corticosteroids (ICS), and an additional drug (usually a long-acting B_2 agonist (LABA)). Additional treatment is considered in these patients, including increasing ICS dosage, or adding a leukotrine receptor antagonist, theophyllines, or slow releasing B_2 agonist tablets.

A small number of patients will continue to remain uncontrolled and will proceed to step 5, which is the addition of frequent or continuous oral corticosteroids (OCS).[2] Treatment at step 5 should use the lowest dose of OCS and consideration should be given to the use of other treatments to minimise the use of OCS.[2] The long term side effects associated with steroids in adults include adrenal suppression, decreased bone mineral density, cataracts and glaucoma.[1] Associated side effects in children also include growth failure and adrenal suppression.[4] In clinical practice, immunosuppressants (methotrexate ciclosporin and oral gold) may be given in adults to decrease the long term use of OCS. However, their efficacy is limited and they all have significant side effects.[2]

Intervention

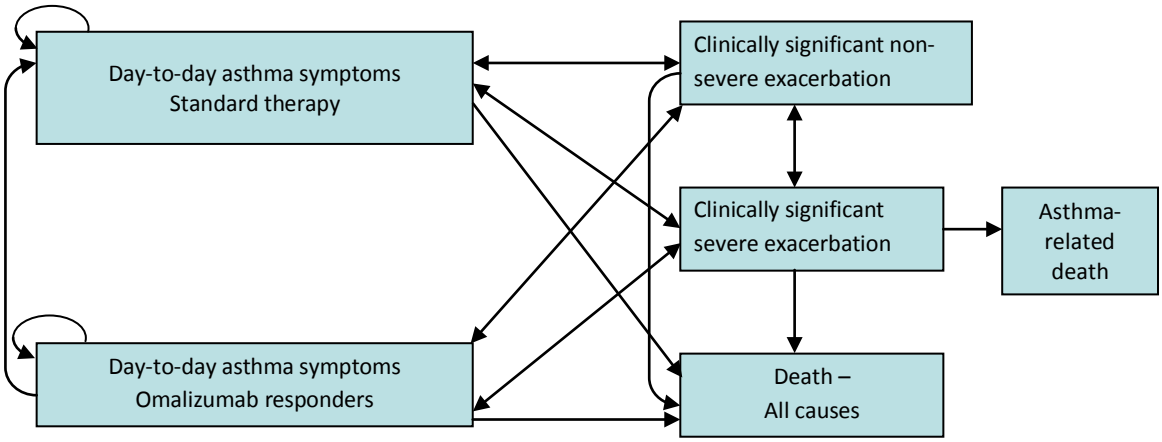
Omalizumab (Xolair) is a recombinant DNA-derived humanised monoclonal antibody that blocks the binding of free serum human IgE to mast cells and basophils, thus inhibiting the release of various inflammatory mediators responsible for allergic asthma symptoms.[5] Omalizumab, given parenterally as a subcutaneous injection every two to four weeks depending on dose, is licensed in adults and adolescents (12 years and older) and in children (6 to <12 years of age) with convincing IgE mediated asthma . Omalizumab is indicated as add-on therapy to improve asthma control in adults and adolescents aged at least 12 years with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.[6] It is also indicated as add-on therapy to improve asthma control in children aged 6 to <12 years with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.[6] The appropriate dose and frequency of administration is determined by baseline IgE measured before the start of treatment, and body weight. Patients whose baseline IgE levels or body weight in kilograms are outside the stated limits should not be given omalizumab.[6]

NICE guidance currently recommends the use of omalizumab for adults and adolescents 12 years and older,[7] but does not currently recommend the use of omalizumab in children aged 6 to 12 years.[4] In contrast, the Scottish Medicines Consortium (September 2007 and March 2010) advise that omalizumab can be used in NHS Scotland as add-on therapy to improve asthma control in children aged 6 to 12 years who are prescribed chronic systemic corticosteroids and in whom all other treatments have failed.[8] In both adults and adolescents and in children omaluzimab may therefore be used either in place of OCS (in addition to step 4 therapy) or in addition to OCS (in addition to step 5 therapy).

Previous NICE appraisals

In the previous appraisals, which informed the NICE technology appraisals TA133 and TA201, evidence on the clinical effectiveness of omalizumab for adults and adolescents was primarily based on the INNOVATE study, which examined the impact of omalizumab as add-on therapy in patients inadequately controlled despite high-dose ICS and LABAs (GINA step 4 treatment).[9] The evidence for children was primarily based on a pre-planned subgroup of children from the IA-05 trial who received concomitant medication (high-dose ICS and LABA).[10] The decision analytic model structure used to assess the cost-effectiveness of omalizumab (see Figure 1) was the same in both appraisals. Treatment effectiveness was based on a reduction in the rate of clinically significant (CS) and severe (CSS) exacerbations (with health-related quality of life (HRQoL) and mortality implications) and different HRQoL for day-to-day asthma symptoms by treatment received.

Figure 1: Schematic of the Markov model used to inform appraisals TA133 and TA201



A number of key areas of uncertainty and potential limitations were identified from the previous appraisals. These include:

1) The relative efficacy and safety of omalizumab compared to OCS has not been addressed. Omalizumab may offer an efficacious alternative to OCS, or reduce the long-term use of OCS, in patients with severe persistent allergic asthma. The efficacy of the two agents and the sparing potential of omalizumab have not been considered to date.

2) Definition of poor asthma control. There is lack of consensus about the definition of poor asthma control in terms of number, type and severity of previous exacerbations and unscheduled hospital admissions.

3) Mortality rates associated with CSS exacerbations. Central to the estimate of cost-effectiveness in TA133 and TA201 was the relationship between mortality associated with CSS exacerbations and patient's age. Evidence to identify the association between number of exacerbations, severity of exacerbations, age and mortality had not been identified systematically in previous appraisals.

4) Improvements in HRQoL with omalizumab. The estimate of cost-effectiveness in TA133 for adults and adolescents was highly sensitive to assumptions about the gain in HRQoL for patients receiving omalizumab. Utility values assigned to omalizumab and standard therapy for day to day asthma symptoms used responses to the Asthma Quality of Life Questionnaire (AQLQ) at week 28 of the INNOVATE trial,[9] mapped these to EQ-5D values and applied them at a constant rate for the duration of treatment. Utility values for clinically significant exacerbations were based on a prospective study and had not been identified systematically in previous appraisals.

5) Adverse effects of omalizumab and/or OCS. The costs and health impact of long-term use of omalizumab on adverse effects or the sparing potential of omalizumab to reduce the long-term adverse effects of OCS have not been modelled in previous appraisals.

6) Duration of treatment with omalizumab. The response rates in clinical practice and the long-term maintenance of response to treatment with omalizumab is unknown. Treatment duration was assumed to be 10 years in TA201 and 5 years in TA133.

It is envisaged that the appraisal of the clinical and cost-effectiveness of omalizumab for the treatment of severe persistent allergic asthma will consider each of these key areas of uncertainty identified by the previous appraisals (TA133 and TA201).

The decision problem will address the effectiveness and cost effectiveness of the addition of omalizumab to optimised standard step 4 or step 5 therapy in patients whose asthma is poorly controlled by that therapy. The decision problem differs depending on whether patients at step 4 or step 5 treatment are considered. For patients at step 4 omalizumab is considered as an alternative to frequent or continuous OCS; in patients at step 5 it is given in addition to frequent or continuous OCS but it may nevertheless allow a reduction in dose of OCS. Avoidance of, or reduction in, OCS is desirable because of the adverse events associated with long-term systemic corticosteroid use.

The appraisal will therefore separately address the efficacy of omalizumab in addition to standard step 4 treatment compared to standard step 4 therapy alone; and in addition to standard step 5 treatment compared to standard step 5 therapy alone. This will include an evaluation of the long-term efficacy and safety of omalizumab at both step 4 and step 5. An evaluation of the adverse effects of omalizumab will also be undertaken. The efficacy and safety of OCS in asthma patients including long-term adverse events (and therefore the benefits of steroid sparing) will also be assessed if possible, as will the efficacy and safety of other comparators where appropriate. The additional areas of uncertainty relating to the relationships between outcome variables and HRQoL identified as arising from TA133 and TA201 will also be considered.

5. Methods for synthesis of clinical evidence

A systematic review of the evidence for the clinical effectiveness and safety of omalizumab for the treatment of severe persistent allergic asthma will be conducted following the general principles recommended in CRD's guidance[11] and the PRISMA statement.[12]

Study selection

Abstracts of identified studies will be independently assessed for inclusion by two reviewers using the criteria outlined below. Disagreements will be resolved through discussion and, where necessary, by consultation with a third reviewer. For studies identified as potentially relevant full papers will also be assessed independently by two reviewers with disagreements resolved by the same procedure.

Inclusion and exclusion criteria

Interventions

Omalizumab given parenterally as a subcutaneous injection every two to four weeks depending on dose in addition to best standard therapy at step 4 or step 5 will be considered (dose and frequency of administration is determined by baseline IgE measured before the start of treatment, and body weight).

Comparators

The direct comparator which will be considered is optimised standard therapy. Standard therapy is step 4 or step 5 treatment. Optimisation of standard therapy is considered to include the elimination of modifiable factors in addition to treatment compliance. As outlined in section 4 the following comparators may be considered:

In adults and children:

(i) Daily high-dose ICS plus a LABA with the possible addition of leukotrine receptor antagonist, theophyllines, or slow releasing B_2 agonist tablets (Step 4).

(ii) Daily high-dose ICS plus a LABA with the possible addition of leukotrine receptor antagonist, theophyllines, or slow releasing B_2 agonist tablets plus frequent or continuous OCS (Step 5).

In adults only the following may be considered if appropriate to UK clinical practice:

Daily high-dose ICS plus a LABA with possible addition of leukotrine receptor antagonist, theophyllines, or slow releasing B_2 agonist tablets plus methotrexate, ciclosporin or gold (Step 4 or step 5)

Participants

Adults and adolescents aged at least 12 years with severe persistent allergic asthma who meet the following criteria:

i) A positive skin test or in vitro reactivity to a perennial aeroallergen.
ii) Reduced lung function (FEV1 < 80%).
iii) Frequent daytime symptoms or night-time awakenings.
iv) Multiple documented severe asthma exacerbations despite daily high-dose ICS plus a long-acting inhaled beta2-agonist.

OR

Children aged between six and 12 years with severe persistent allergic asthma who meet the following criteria:

i) A positive skin test or in vitro reactivity to a perennial aeroallergen.
ii) Frequent daytime symptoms or night-time awakenings.
iii) Multiple documented severe asthma exacerbations despite daily high-dose ICS plus a long-acting inhaled beta2-agonist

Subgroups

Analysis of specific subgroups will be undertaken where sufficient data are available. These may include:

(i) subgroups defined by the degree of poor asthma control in terms of number, type and severity of exacerbations, including hospitalisation for an asthma exacerbation.
(ii) subgroups defined according to treatment received, for example, whether or not patients are receiving a maintenance dose of OCS.

Outcomes

Outcomes which will be considered include asthma symptoms, incidence of clinically significant exacerbations, incidence of severe exacerbations which require unscheduled contact with healthcare professionals or hospitalisations, mortality, use of OCS, time to discontinuation of treatment, adverse effects of treatment including allergic reactions (anaphylaxis), and health related quality of life. It is anticipated that measurement and definitions of outcomes and, in particular, of asthma symptoms, exacerbations and severe exacerbations may vary between studies; a pragmatic approach to this heterogeneity will be adopted. In order to consider the full impact of omalizumab, the effects of steroid-sparing on quality of life and reduced steroid-associated adverse events will be considered. These steroid-related adverse events may include bone outcomes including fracture; incidence of infectious disease, hypertension, ocular outcomes including cataracts and glaucoma and, in children and adolescents, growth retardation.

Study design

The review of omalizumab will include randomised controlled trials (RCTs) with a placebo or active comparator. Data from cohort studies may also be considered in order to provide data on longer term response and adherence to treatment.

For the assessment of long-term adverse events which may occur beyond the duration of the RCTs, data from the FDA and EMA websites and existing reviews will be considered in the first instance. Data from cohort studies, continuation studies and post-marketing surveillance will be considered if necessary.

Data extraction

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

Quality assessment

The quality of RCTs and other study designs will be assessed using standard checklists.[11] In the case of non-randomised studies, tools used by the TAR group in previous reviews will be employed. Systematic reviews will be appraised using DARE criteria. The assessment will be performed by one reviewer, and independently checked by a second. Disagreements will be resolved through consensus, and if necessary, a third reviewer will be consulted.

Methods of analysis and synthesis

In the first instance the results of the data extraction and quality assessment will be presented in a series of structured tables and summarised narratively. Where there are sufficient clinically and statistically homogeneous data, efficacy and safety data from RCTs comparing omalizumab in addition to standard therapy with standard therapy at step 4 or step 5 alone will be pooled using appropriate meta-analytic techniques.

While it is anticipated that the majority of the trial evidence will have evaluated the effect of add-on omalizumab compared with placebo in patients who are inadequately controlled despite step 4 therapy, trials conducting head-to-head comparisons of add-on omalizumab with optimised standard treatment at step 5 of the ‘British guideline on the management of asthma’, namely OCS in addition to ICS, may not be available. Therefore, if feasible and

appropriate, indirect evidence will be sought to evaluate the efficacy of omalizumab compared with OCS. If an indirect link cannot be established from RCT evidence, further studies tailored towards evaluating the efficacy of omalizumab in patients requiring OCS will be used to examine the steroid sparing effects of omalizumab, data availability permitting.

Data relating to children aged under 12 years will be analysed separately to that for adults and adolescents aged at least 12 years. Where possible, separate subgroup analyses for adults and for adolescents may be undertaken. Clinical, methodological and statistical heterogeneity will be investigated using appropriate techniques.

Additional questions

The decision problem has identified important issues in addition to the central questions of the efficacy and safety of omalizumab and its comparators. Primarily these relate to the impact of steroid sparing on other outcomes including quality of life and adverse events. This will be addressed using studies of patients with asthma wherever possible. Analysis of the impact of other potential steroid sparing comparators, methotrexate and ciclosporin on these outcomes, will be undertaken where sufficient data are available.

The relationships between asthma symptoms, exacerbations and severe exacerbations, and quality of life; and between asthma exacerbations and severe exacerbations and mortality will also need to be addressed in order to inform the assessment of cost-effectiveness (see section 6 below).

Comprehensive reviews will not necessarily be conducted in order to address these questions, but the best and most appropriate evidence will be sought using systematic methods. In the first instance existing systematic reviews, suitable good quality UK studies and references cited in the SIGN and GINA guidelines will be used. A narrative synthesis will be produced to summarise the best available evidence for these questions.

Search strategy

A number of searches of electronic databases will be conducted in order to inform the different aspects of the decision problem. Appropriate strategies will be developed to identify studies in each case.

For the primary question of the efficacy of omalizumab, searches of electronic databases will be conducted to identify relevant RCTs and systematic reviews. In addition, relevant published systematic reviews and trial registers will be searched to identify any further RCTs of relevance. Information on adverse events of omalizumab will be identified from searching

resources of the US and European drug regulatory agencies (i.e. FDA, EMA). Where further information is required, additional searches for evidence on serious adverse events will be undertaken. No language restrictions will be applied to the search strategy. Additional searches will be undertaken where required for the assessment of clinical or cost effectiveness.

A list of databases which will be searched is provided in the appendix.

The searches for the information to inform the additional questions and reviews required for the economic model will be will be designed pragmatically to capture relevant information to inform model parameters as necessary.

At the time of receiving the company submission, update searches will be conducted to ensure the review remains up-to-date and covers all relevant evidence at the time of submission. Handsearching of new volumes of key journals (to be defined in consultation with the clinicians) will be undertaken to ensure the searches remain up to date.

Reference management and documentation

As several databases will be searched, some degree of duplication will result. In order to manage this issue, the titles and abstracts of bibliographic records will be downloaded and imported into Endnote bibliographic management software to remove duplicate records. Full details of the searching process will be recorded.

6. Methods for synthesis of cost effectiveness

The sources detailed in Section 5 will be used to identify studies of the cost-effectiveness of omalizumab. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature. The quality of the cost-effectiveness studies will be assessed according to a checklist updated from that developed by Drummond et al.[13]This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Health and Clinical Excellence (NICE).[14] This information will be tabulated and summarised within the text of the report. In particular, information will be extracted on the

comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs (medical and non-medical) and productivity costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic / probabilistic sensitivity analysis).

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the specific research question posed and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review.

As discussed in section 4, a number of key areas of uncertainty were identified in the review process of TA133 and TA201, which the current assessment will attempt to address where sufficient data are available. It is anticipated that two additional reviews will be undertaken to inform the economic evaluation of omalizumab:

1. The link between asthma exacerbations, hospitalisations and mortality. For the cost-effectiveness assessment in TA133 and TA201, mortality associated with clinically significant exacerbations was a key driver of the cost-effectiveness of omalizumab. Since data on mortality had not been identified systematically in the previous appraisals, a systematic search will be undertaken to identify the association between asthma-related mortality, number and severity of exacerbations and hospitalisations in the UK.
2. HRQoL associated with severe persistent allergic asthma. Since the utility values for clinically significant exacerbations and day to day asthma symptoms on treatment with omalizumab and standard therapy had not been identified systematically in the previous appraisals, full systematic searches of the literature will be carried out to inform the HRQoL experienced by asthma patients for incorporation into the decision analytic model. In accordance with the NICE reference case, the inclusion criteria for studies will be restricted to those which report data based on the EuroQoL – EQ5D instrument (either directly or via a mapping algorithm).

Development of a new decision-analytic model

A new decision-analytic model will be developed to estimate the cost-effectiveness of omalizumab as an add-on therapy to optimised standard therapy of severe persistent allergic asthma. The model will be developed in accordance with the NICE reference case. The perspective will be that of the National Health Services and Personal Social Services. Productivity costs are not included within this perspective but may be included as a secondary analysis. Both cost and QALY will be discounted at 3.5%.

Where sufficient data is available, the cost-effectiveness assessment will aim to determine the optimal positioning of omalizumab within the overall stepwise treatment approach to asthma described in section 4. Omalizumab has a potential dual role in the stepwise management of severe persistent allergic asthma: (i) as a replacement for OCS; or (ii) used in conjunction with OCS, with a view to reducing the maintenance dose of OCS. The appropriate comparators will depend on the positioning of omalizumab as either an addition to step 4 optimised therapy or as an alternative to step 5 (optimised therapy plus regular OCS or other treatments as appropriate). The model will consider the long-term prognosis of severe persistent allergic asthma in order to capture the long-term costs and consequences associated with the natural history of these patients in the absence of omalizumab. In projecting to the lifetime of patients, assumptions concerning the duration of treatment and the duration of the effect of treatment need to be made. These assumptions will be informed by expert clinical opinion and varied to examine the sensitivity of the results to alternative durations of treatment.

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise patients' care and subsequent prognosis and the impacts of alternative therapies (including long-term use of OCS), in a way that is clinically acceptable.
- To populate this model using the most appropriate data identified systematically from a series of inter-related reviews using published literature and routine data sources.
- To relate intermediate outcomes to final health outcomes, expressed in terms of quality-adjusted life years (QALYs). This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources.
- To estimate the mean cost-effectiveness of omalizumab (in addition to best standard therapy) compared with best standard therapy without omalizumab, based on an

assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival.

- Consistent with available evidence, to report cost-effectiveness of alternative treatments for specific sub-groups of patients, such as those with a recent hospitalisation for an asthma exacerbation.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this *parameter uncertainty,* is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, *decision uncertainty.* This is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.
- To inform future research priorities in the NHS, the model will be used to undertake analyses of the expected value of perfect information. These take the decision uncertainty associated with analysis and quantify the cost of this uncertainty in terms of health gain forgone and resources wasted by making the wrong decision. This cost of uncertainty represents the value of perfect information, and this can be estimated for the model overall and for individual parameters.

7. Handling the company submission

All data submitted by the drug manufacturers will be considered if received by the review team no later than 19th January 2012. Data arriving after this date will only be considered if time constraints allow. If efficacy and/or adverse effects data meet the inclusion criteria for the review then they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission 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. An assessment of any differences between the published economic evaluations, those submitted by the manufacturers and any economic evaluation developed by us will be reported.Any

'commercial in confidence' data taken from a company submission will be clearly marked in the NICE report (*underlined and followed by an indication of the relevant company name e.g. in brackets)* and removed from the subsequent submission to the HTA.

8. Competing interests of authors

None of the authors have any competing interests to declare.

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Appendix

Databases which will be searched:

For RCTs: MEDLINE, MEDLINE In-Process, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL);

For ongoing trials: ClinicalTrials.gov and Current Controlled Trials;

For economic evaluations: NHS Economic Evaluation Database (NHS EED) and EconLit;

For conference proceedings: Conference Proceedings Citation Index - Science (CPCI-S)