Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence – FINAL PROTOCOL

May 4th 2006

1. Title of the project

Inhaled corticosteroids and long acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years

2. Name of TAR teams and 'leads'

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3. Plain English Summary

Chronic asthma is a condition that affects around 5 million children and adults in the UK. The symptoms can include wheezing, shortness of breath, and general difficulties in breathing, and can significantly disrupt daytime activity and the ability to sleep well at night. Symptoms occur as a result of tightening of the muscles surrounding the airways and inflammation of the airway lining. People with asthma need to maintain good control of the condition to prevent worsening of symptoms or 'asthma attacks'. This can be achieved by following a healthy lifestyle, reducing contact with substances likely to aggravate asthma, and regular and correct use of prescribed drugs. People with mild asthma can usually manage the condition through use of an inhaler device containing a short acting $beta_2$ agonist (e.g. salbutamol) on an as needed basis. Short acting $beta_2$ agonists are known as bronchodilators and work by relaxing the airway muscles to improve the passage of air into the lungs. When this is not enough to prevent worsening of symptoms patients may be prescribed one of the five available corticosteroids, usually via a hand-held inhaler. A corticosteroid works to reduce inflammation in the airways. The corticosteroid is usually inhaled twice a day for a given period of months or longer (in addition to the inhaled short acting $beta_2$ agonist, as needed) until asthma is stabilised, at which time it may be gradually reduced. Often a low, regular dose of inhaled corticosteroid is needed to control symptoms.

Where asthma symptoms continue to be difficult to control the daily dose of inhaled corticosteroid may be increased, or a third drug may be prescribed. Inhaled long acting $beta_2$ agonists, of which there are two, are commonly used in these situations. They may be given separately or in a combined inhaler containing the inhaled corticosteroid. Other drugs may be given in cases where control is still not adequate.

There are a number of different inhaled corticosteroids and long acting $beta_2$ agonists available, in different combinations and via different inhalers. This study will systematically summarise the results of clinical trials which compare the different inhaled corticosteroids with each other; trials which compare inhaled corticosteroids combined with long acting $beta_2$ agonists with use of inhaled corticosteroids only; and trials which compare the two different combinations of inhaled corticosteroids and long acting $beta_2$ agonists. The report will include an economic evaluation, to compare the costs and benefits of the different drugs to indicate whether they represent good value for money from the NHS and personal social services perspective.

4. Decision problem

The aim of this health technology assessment is to assess the clinical-effectiveness and cost-effectiveness of inhaled corticosteroids (ICS), and inhaled corticosteroids in combination with long acting $beta_2$ agonists (LABA), in the treatment of chronic asthma in children aged under 12 years.

4.1 Background to asthma

Asthma is a condition characterised by inflammation and narrowing of the bronchial airways leading to wheezing, cough, chest tightness, shortness of breath and general difficulties in breathing. Symptoms vary from mild intermittent wheezing or coughing to severe attacks requiring hospital treatment. Severity can be defined on the basis of symptoms, lung function, and incidence of exacerbations. Definitions vary but a classification system has been proposed by the Global Initiative for Asthma (GINA)[1,2]. Asthma can be triggered by a number of stimuli, including allergens (e.g. animals, house dust mite), environmental factors (e.g. dust, pollution, tobacco smoke) and exercise. Family history of asthma and low birth weight may pre-dispose people to the condition. Other risk factors include increasing age, lower social class, and urban dwelling[3]. Although common in children and young adults, asthma can affect people at any time of life.

Asthma is distinguished from other related conditions such as chronic obstructive pulmonary disease (COPD) or emphysema through reversible rather than progressive airway narrowing (although evidence is emerging that people with asthma do have some degree of decline in lung function over time). In young children it is often not possible to measure lung function in order to confirm variable airway obstruction; diagnosis is then usually made on careful clinical history and examination

Prevalence has increased considerably over recent decades, in both developed and developing countries. Reasons are complex, reflecting environmental and lifestyle factors. In the UK there are 5.2 million people (9%) with asthma, including 590,000 teenagers. In England and Wales the number of people affected is around 4.7 million. Whilst severe exacerbations of asthma may cause death, mortality from the condition is relatively low compared to other respiratory diseases such as COPD. Respiratory disease accounts for greater mortality in the UK (24% of total deaths) than coronary heart disease (21%) or non-respiratory cancer (19%). However, asthma is responsible for only 1% of respiratory deaths[3].

4.2 Management

The management of asthma includes several inter-linked approaches including medication (e.g. (bronchodilators, corticosteroids), lifestyle modification, environmental changes (e.g. minimising the impact of allergens in the home or workplace), patient education (e.g. to encourage self-management and improve concordance with medication), and regular monitoring to assess disease control. Management is primarily the responsibility of the general practitioner in collaboration with the patient, although specialist intervention may be required in severe cases. The aims of treatment are to relieve symptoms (e.g. wheeze, cough), improve health related quality of life (including ability to work, study or sleep), improve lung function (i.e. Forced Expiratory Volume 1, (FEV_1); Peak Expiratory Flow Rate, (PEFR)), minimise the requirement for relief (e.g. short acting $beta_2$ agonists) and rescue (oral corticosteroids) medication and reduce adverse effects associated with medication.

The British Thoracic Society (BTS), in collaboration with the Scottish Intercollegiate Guidelines Network (SIGN), have published clinical guidelines on asthma [4,5]. The guidelines cover a variety of aspects of management, including pharmacological management. They propose a stepwise approach to achieving symptom control (Appendix 9.1). Treatment is initiated at the step most appropriate to the initial severity of asthma and the person's day to day needs, with the aim of achieving early control of symptoms. Control is maintained by stepping up treatment as necessary and stepping down when control is good.

First line treatment in mild intermittent asthma is with an inhaled short acting $beta_2$ agonist, as required for symptom relief (e.g. salbutamol, or terbutaline). Treatment is stepped up with the introduction of regular preventer therapy with ICS in addition to symptomatic use of an inhaled short acting $beta_2$ agonist (Step 2). If necessary a long acting $beta_2$ agonist (LABA) is added (but not in children under the age of four in whom a leukotriene receptor agonist should be considered, and in children under 2 years referral to a respiratory paediatrician should be considered) (Step 3). If control is still not adequate the dose of the inhaled corticosteroid can be increased, in addition to introduction of a fourth drug such as an theophylline or a leukotriene receptor agonist (children aged 5 to 12) (Step 4). For children aged under 5 years, Step 4 involves referral to a respiratory paediatrician. For children aged 5 to 12, if response remains poor specialist care may be initiated with regular use of oral corticosteroids (e.g. prednisolone), in addition to the other drugs (Step 5).

In 2000 NICE issued guidance to the health service in England and Wales on the use of inhaler devices in children with chronic asthma aged under five (Guidance number 10), and in 2002 guidance for older children (aged 5-15, Guidance number 38).

For children under the age of 5 years with chronic stable asthma both corticosteroids and bronchodilator therapy should be routinely delivered by a pressurised metered dose inhaler (pMDI) and a spacer system, with a facemask where necessary. Where this combination is not clinically effective for the child and depending on the child's condition, nebulised therapy may be considered. In the case of children aged 3 to 5 years, a dry powder inhaler (DPI) may also be considered.

For children aged 5 to 15 years a press-and-breathe pressurised metered dose inhaler (pMDI) and suitable spacer device is recommended as the first-line choice for the delivery of inhaled corticosteroids. If adherence is likely to be poor then other alternatives should be considered. For bronchodilators a wider range of devices should be considered to take account of their more frequent spontaneous use, the greater need for portability, and the clear feedback that symptom response provides to the device user. Over-arching principles when choosing an inhaler include the therapeutic need for the particular drug, the ability of the child to develop and maintain an effective technique with the specific device, the suitability of a device for the child's and carer's lifestyles, considering factors such as portability and convenience and the child's preference for and willingness to use a particular device.

A planned update of both sets of guidance in 2005 was not undertaken as it was found that little new evidence had emerged since the first guidance. They have both now been moved to the Institute's 'static' list of appraisals, which will not routinely be updated.

4.2.1 Inhaled corticosteroids (ICs)

ICS work to reduce bronchial inflammation. They are recommended for prophylactic treatment of asthma when patients are using a short acting $beta_2$ agonist more than three times a week or if symptoms disturb sleep more than once a week, or if the patient has suffered exacerbations in the last two years requiring a systemic corticosteroid or a nebulised bronchodilator. Corticosteroid inhalers should be used regularly for maximum benefit.

There are currently 3 ICS licensed in the UK for children (see Appendix 9.2 for details of delivery devices. NB. High dose inhalers are not licensed in children):

- beclometasone dipropionate (AeroBec [3M], Asmabec Clickhaler [Celltech], Beclazone Easi-Breathe [IVAX], Becloforte [Allen & Hanburys], Beclometasone Cyclocaps [APS], Becodisks [Allen & Hanburys], Becotide [Allen & Hanburys], Easyhaler [Ranbaxy], Filair [3M], Pulvinal Beclometasone Dipropionate [Trinity])
- budesonide (Budesonide Cyclocaps [APS], Easyhaler [Ranbaxy], Novolizer [Viatris], Pulmicort [AstraZeneca])
- fluticasone propionate (Flixotide [Allen & Hanburys])

Beclometasone dipropionate, budesonide and fluticasone propionate have been used for some time, whilst ciclesonide is relatively newer. Ciclesonide (Alvesco [Altana]) is included in the scope issued by NICE with the expectation that it may receive an extension to its marketing authorisation to include children under the age of 12 within the time frame for the appraisal. There are a variety of delivery systems including pressurised metered-dose inhalers (pMDI), breath-activated pMDIs, dry powered formulations, and nebulisers. Chlorofluorocarbons (CFCs) have been the traditional propellant in pMDIs, but with the phasing out of CFCs they are being replaced by ozone-friendly hydrofluoroalkanes (HFAs). Spacer chambers can be attached to pMDIs to make them easier to use and improve drug delivery to the lungs.

Standard daily recommended doses of ICS in children are 100 micrograms (mcg) twice daily for budesonide and beclometasone dipropionate; and 50 mcg twice daily for fluticasone propionate[6]. The BTS recommends titrating to the lowest dose at which effective control is maintained[5,7]. In children this can be up to 400 mcg per day (for budesonide or beclometasone dipropionate)[5]. Fluticasone is considered clinically equivalent to budesonide or beclometasone dipropionate at half the dose. (However, HFA propelled beclometasone dipropionate is regarded as clinically equivalent to fluticasone at the same dose).

If maintenance therapy with an ICS does not adequately control symptoms there are a number of potential treatment options. One is to continue with the IC but to increase the dose to the higher end of the recommended range (e.g. up to 400 mcg in children aged 5 to 12 years, or 200mcg in children younger than 5 years). However, this increases the risk of adverse effects (such as growth and adrenal suppression). An alternative is to add a LABA to ICs (but not in children younger than 4 years old). Adding a LABA may be preferential as results of dose-response studies suggest that higher doses of ICS may worsen the overall therapeutic ratio (that is, the ratio of the maximally tolerated dose of a drug to the minimally curative or effective dose)[8].

4.2.2 Long acting beta$_2$ agonists (LABA)

Two LABAs are licensed for use in the UK, salmeterol (Serevent) and formoterol (Foradil; Oxis). Like short acting beta$_2$ agonists, LABAs have a bronchodilatory action, expanding the bronchial airways to improve the passage of air. They are recommended in addition to existing inhaled corticosteroid therapy, rather than replacing it. They can be used in combination with inhaled corticosteroids in separate inhalers, or combined in one inhaler. There are two licensed combination inhalers in the UK:

- budesonide + formoterol fumarate (Symbicort)

- fluticasone propionate + salmeterol (as xinafoate) (Seretide)

Budesonide and formoterol fumarate can be used only in children over six years, whilst fluticasone propionate and salmeterol can be used in children as young as four. The two LABAs differ chemically, with formoterol associated with a more rapid onset of action.

A typical dose of fluticasone propionate/salmeterol in children over four is 100/50 micrograms (mcg) per day, titrated up to 200/100 mcg per day if necessary. A typical dose of budesonide/formoterol in children over six is 80/4.5 mcg once daily, titrated up to 320/18 mcg per day in severe cases.

Given the vast range of options available in the pharmacological management of chronic asthma, an assessment of clinical-effectiveness and cost-effectiveness of the various strategies is required. Specifically, an assessment is needed of the relative benefits and adverse effects of the different ICS; and of the two ICS and LABA combination inhalers. It is also necessary to assess the benefits and adverse effects of combined treatment with an ICS and a LABA compared with continuing ICS alone (including increasing the dose of the ICS) in situations of worsening asthma control.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy

- A search strategy will be devised and tested by an experienced information scientist. The strategy will be designed to identify two different types of study: (i) studies reporting the clinical-effectiveness of inhaled corticosteroids and long acting $beta_2$ agonists; and (ii) studies reporting the cost-effectiveness of inhaled corticosteroids and long acting $beta_2$ agonists. The draft search strategy for Medline is in Appendix 9.3.
- A number of electronic databases will be searched including: The Cochrane Database of Systematic Reviews (CDSR); The Cochrane Central Register of Controlled Trials; NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE) and the NHS Economic Evaluation Database (NHS EED); Medline (Ovid); Embase (Ovid); National Research Register; Current Controlled Trials; ISI Proceedings; Web of Science; and BIOSIS. Bibliographies of related papers will be assessed for relevant studies where possible.
- The manufacturers' submissions to NICE will be assessed for any additional studies.
- Experts will be contacted to identify additional published and unpublished references.
- Searches will be carried out from the inception date of the database until February/March 2006 (for clinical-effectiveness and cost-effectiveness studies). All searches will be limited to the English language. The searches will be updated around October 2006.

- Searches for other evidence to inform cost-effectiveness modelling will be conducted as required (see Section 6.5b).

5.2 Inclusion and exclusion criteria

5.2.1 Intervention

Studies reporting evaluations of the following inhaled corticosteroids will be included:

- beclometasone dipropionate
- budesonide
- ciclesonide*
- fluticasone propionate

*subject to licensing

Studies reporting evaluations of the following inhaled corticosteroids combined with long acting $beta_2$ agonists in the same inhaler (i.e. combination inhalers) will be included:

- budesonide + formoterol fumarate (in children aged 6 and over)
- fluticasone propionate + salmeterol (as xinafoate) (in children aged 4 and over)

- Studies reporting treatment duration of four weeks or less will not be included.

5.2.2 Comparators

- The inhaled corticosteroids will be compared with each other.
- The combination inhalers will be compared with: each other; and with inhaled corticosteroids only. They will also be compared with inhaled corticosteroids and long acting $beta_2$ agonists administered separately in terms of any adverse events likely to impact on costs and cost effectiveness.
- Studies testing different doses of the same agent, or the same agent delivered by different inhaler devices will not be included.

5.2.3 Types of studies

- Fully published randomised controlled trials (RCTs) or systematic reviews of RCTs. Double blinding is not a pre-requisite for inclusion, although blinding will be assessed as part of critical appraisal (see Section 5.3). Indicators of a ‘systematic’ review include: an explicit search strategy, and inclusion/exclusion criteria.

- Studies published as abstracts or conference presentations from 2004 onwards will be included in the primary analysis of clinical and cost-effectiveness only if sufficient details are presented to allow an appraisal of the methodology and assessment of results.

5.2.4 Population

- Children aged under 12 years with chronic asthma. Studies in which the patient group is asthmatics with a specific related co-morbidity (e.g. cystic fibrosis) will not be included.
- Where data are available clinical-effectiveness and cost-effectiveness will be reported for patient sub-groups, in terms of disease severity and age. Concordance according to different patient sub-groups will be assessed where data allow.
- Studies reporting the treatment of acute exacerbations of asthma will not be included.

~~5.2.4~~5.2.5 Outcomes

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- Studies reporting one or more of the following outcomes will be included:
  - objective measures of lung function (e.g. FEV_1, PEFR)
  - symptom-free days and nights
  - incidence of mild and severe acute exacerbations (e.g. mild – requiring unscheduled contact with healthcare professional; severe – requiring hospitalisation, short-term 'rescue' use of systemic corticosteroids or visit to accident and emergency department).
  - adverse effects of treatment (e.g. growth suppression)
  - health-related quality of life
  - mortality

- Titles and abstracts of studies identified by searching will be screened by one reviewer based on the above inclusion/exclusion criteria. A second reviewer will check a random 10% of these with any discrepancies resolved through discussion and involvement of a third reviewer where necessary.
- Full papers of studies which appear potentially relevant on title or abstract will be requested for further assessment. All full papers will be screened independently by one reviewer and checked by a second, and a final decision regarding inclusion will be agreed. Any discrepancy will be resolved by discussion with involvement of a third reviewer where necessary.

5.3 Critical appraisal and data extraction

- A number of recently updated Cochrane systematic reviews of the effectiveness of comparisons of ICS[9-11], and ICS with LABA[12] have been published. Where possible these and other high quality systematic reviews will be used to assess clinical-effectiveness. RCTs published since the reviews were last updated would be prioritised for full data extraction and critical appraisal. The

findings of the systematic reviews and the supplemental RCTs will be used together to inform the assessment of clinical effectiveness.

- Data extraction and critical appraisal will be performed by one reviewer using a standardised data extraction form (see Appendix 9.4). A second reviewer will check the form for accuracy and completeness. Discrepancies will be resolved by discussion, with involvement of a third reviewer where necessary.
- The quality of included RCTs and systematic reviews will be assessed using NHS CRD (University of York) criteria[13] (see Appendix 9.5).

~~5.3~~5.4 Methods of analysis/synthesis

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- Clinical-effectiveness studies will be synthesised through a narrative review with tabulation of results of included studies.
- Where data are of sufficient quantity, quality and homogeneity, a meta-analysis of the clinical-effectiveness studies will be performed, using appropriate software.
- To minimise clinical heterogeneity the synthesis will seek to group together studies reporting similar populations and interventions.
    - For example, comparisons of different ICS delivered via pMDI may be considered separately to those comparing different ICS delivered by dry powder formulations.
    - Similarly, comparisons of ICS where a CFC propelled pMDI is used may be grouped separately to those where the propellant is HFA, given suggested differences in potency[11]
    - Dose equivalence will need to be taken into account as far as the evidence allows, particularly where a study compares a CFC pMDI ICS with a HFA pMDI ICS.

6. Methods for synthesising evidence of cost-effectiveness

6.1 Search strategy

Refer to Appendix 9.3 for details of the draft search strategy for Medline. The sources to be searched are similar to those used in the clinical-effectiveness review (see Section 5.1). All searches will be limited to the English language.

6.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical to those for the systematic review of clinical effectiveness, except that:

- non-randomised studies may be included (e.g. decision model based analyses or analyses of patient-level cost and effectiveness data alongside observational studies);
- full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost-consequence analyses will be included. (Economic evaluations which only report average cost-effectiveness

ratios will only be included if the incremental ratios can be easily calculated from the published data);

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

6.3 Study quality assessment

The methodological quality of the economic evaluations will be assessed using accepted frameworks such as the International consensus-developed list of criteria developed by Evers and colleagues (2005)[4], and Drummond and colleagues (1997)[14]. For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling (Philips and colleagues, 2004)[15]. We will examine recent published studies which are carried out from the UK NHS and PSS perspective in more detail.

6.4 Data extraction strategy

Data will be extracted by one researcher into two summary tables: one to describe the study design of each economic evaluation and the other to describe the main results.

- The following data will be extracted into the study design table: author and year; model type or trial based; study design (e.g. cost-effectiveness analysis (CEA) or cost-utility analysis (CUA)); service setting/country; study population; comparators; research question; perspective, time horizon, and discounting; main costs included; main outcomes included; sensitivity analyses conducted; and other notable design features.
- For modelling-based economic evaluations a supplementary study design table will record further descriptions of model structure (and note its consistency with the study perspective, and knowledge of disease/treatment processes), sources of transition and chance node probabilities, sources of utility values, sources of resource use and unit costs, handling of heterogeneity in populations and evidence of validation (e.g. debugging, calibration against external data, comparison with other models).
- For each comparator in the study, the following data will be extracted into the results table: incremental cost; incremental effectiveness/utility and incremental cost effectiveness ratio(s). Comparators excluded on the basis of dominance or extended dominance will also be noted. The original authors' conclusions will be noted, and also any issues they raise concerning the generalisability of results. Finally the reviewers' comments on study quality or generalisability (in relation to the NICE scope) will be recorded.

6.5 Synthesis of evidence on costs and effectiveness

(a) Published and submitted economic evaluations

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base from published economic evaluations and sponsor submissions to NICE

(b) Economic Modelling

A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and Personal Social Services using a decision analytic model. The evaluation will be constrained by available evidence. If possible, the incremental cost-effectiveness of the intervention drug classes and the specified comparators will be estimated in terms of cost per Quality Adjusted Life Year (QALY) gained, as well as the cost per acute exacerbation avoided.

Model structure will be determined on the basis of research evidence and clinical expert opinion of:

- The biological disease process of chronic asthma in children (i.e. knowledge of the natural history of the disease);
- The main diagnostic and care pathways for patients in the UK NHS context (both with and without the intervention(s) of interest); and
- The disease states or events that are most important in determining patients' clinical outcomes, quality of life and consumption of NHS or PSS resources.

For example, we will need to consider developing a natural history model of chronic asthma which could reflect factors such as: patient age, asthma severity (e.g. FEV_1, PEF, frequency of acute exacerbations), whether their asthma is predominantly self-managed or GP/primary care nurse-managed. The extent to which the model *is able to* fully reflect these various factors will depend upon the available research literature. The extent to which the model *needs to* reflect these factors will depend on how plausible it is that they impact on either the effectiveness or cost impacts of the interventions.

Parameter values will be obtained from relevant research literature, including our own systematic review of clinical-effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group we may use data from sponsor submissions to NICE or expert clinical opinion. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS in 2005 (this is the most recent year for which NHS National Schedule of Reference Cost data will be available). Cost data will be identified from NHS and PSS reference costs or, where these are not relevant, they will be extracted from published work or sponsor submissions to NICE as appropriate. If insufficient data are retrieved from published sources, costs may be obtained from individual NHS Trusts or groups of Trusts.

To capture health-related quality of life effects, utility values will be sought either directly from the relevant research literature. Ideally utility values will be taken from studies that have been based on "public" (as opposed to patient or clinician) preferences elicited using a choice-based method.

Analysis of uncertainty will focus on cost-utility, assuming the cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented both using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

The simulated population is likely to be separate birth cohorts of children aged between 2 and 11 years of age. Where possible the base case results will be presented separately for grouped age-bands, at least for 2- to 4-year-olds and 5- to 11-year-olds. The time horizon for our analysis will be between 1 and 5 years; sufficiently long to reflect both the chronic nature of the disease and estimate differences in rare outcomes, such as asthma-related deaths.

Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be conducted as required (e.g. health related quality of life; epidemiology and natural history). This is in accordance with the methodological discussion paper produced by InterTASC (January 2005).

7. Handling the company submission(s)

All information submitted by the manufacturers/sponsors as part of the NICE appraisal process will be considered if received by the TAR team no later than 2nd August 2006. Information arriving after this date will not be considered.

Economic evaluations included in sponsors' submission will be assessed against the NICE guidance for the Methods of Technology Appraisals (NICE, 2004) and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used.

Incremental cost effectiveness ratios (ICERs) estimated from consultee models will be compared with results from the Assessment Group's analysis, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

Any 'commercial in confidence' data taken from a company submission will be <u>underlined</u> and highlighted in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8. Competing interests of authors

There are no competing interests

9. Appendices

9.1. SIGN/BTS Pharmacological management pathway for chronic asthma

9.2. Inhaled steroids and devices

9.3 Medline search strategy

9.4. Data extraction form (RCTs and systematic reviews)

9.5 Quality assessment criteria (RCTs and systematic reviews)

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11. Timetable/milestones

- Progress report to be submitted to NCCHTA – 9th August 2006
- Assessment Report to be submitted to NICE/NCCHTA – 20th December 2006

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Appendix 9.1 SIGN/BTS Pharmacological management pathway for chronic asthma

Step 1 – Mild intermittent asthma

Occasional inhaled short acting beta$_2$ agonists used as required for symptomatic relief.

Step 2 – Introduction of regular preventer therapy

Inhaled corticosteroids are the recommended preventer drugs for achieving overall treatment goals. Although a precise threshold for initiating inhaled corticosteroids has not been established, the guideline recommends that they are initiated in the following circumstances:

- exacerbations of asthma in the last two years
- using inhaled short-acting $beta_2$ agonists three times a week or more
- symptomatic three times a week or more, or waking one night a week.

Other, less effective, preventer therapies include cromones (sodium cromoglycate, or nedocromil sodium), leukotriene receptor antagonists (montelukast) and theophyllines (aminophylline and theophylline). In children who cannot take an inhaled corticosteroid, a leukotriene receptor antagonist should be used.

Step 3 – Add-on therapy

There is no precise threshold in terms of dose of inhaled corticosteroid for the introduction of a third drug. However, the guidelines recommend a trial of add-on therapy before increasing the daily dose of inhaled corticosteroid above 400 micrograms[1] in children (5-12 years). Options for add-on therapy in children taking doses of 400 micrograms are as follows.

- In children aged 5-12 years, the addition of an inhaled long-acting $beta_2$ agonist is the first choice. (Neither of the long-acting $beta_2$ agonists is licensed for use in children under the age of 4 years.)
- In children aged 2-5 years, a leukotriene receptor antagonist should be considered.
- In children aged under 2 years, referral to a respiratory paediatrician should be considered if the diagnosis is unclear or in doubt or if there is a failure to respond to conventional treatment.

Step 4 – Poor control on moderate dose of inhaled steroid plus add-on therapy: addition of fourth drug (children aged 5-12 years).

For children aged under 5 years, step 4 is referral to a respiratory paediatrician.

In children aged 5-12 years, if control remains inadequate on inhaled corticosteroids at daily doses of 400 micrograms plus add-on therapy the following options should be considered:

- increasing the daily dose of inhaled corticosteroids to 800 micrograms
- leukotriene receptor antagonists
- theophyllines

[1] Doses refer to beclometasone dipropionate given via a pressurised metered-dose inhaler. Adjustment is necessary for fluticasone and some alternative delivery devices.

Step 5: (for children aged 5-12 years only) continuous or frequent use of oral corticosteroids. Before proceeding to this step, referral to specialist care should be considered.

Appendix 9.2- Drugs and devices

Inhaled steroids

Drug	Device type	Name	Manufacturer
beclometasone dipropionate	pMDI (CFC)	AeroBec Forte Autohaler®	3M
		Becloforte	Allen & Hanburys
		Becotide	Allen & Hanburys

		Filair	3M
		Filair Forte	3M
	pMDI (HFA)	Qvar Autohaler®	3M
	Dry powder	Asmabec Clickhaler ®	Celltech
		Beclometasone cyclocaps Cyclohaler®	APS
		Becodisks Diskhaler®	Allen & Hanburys
		Easyhaler	Ranbaxy
		Pulvinal Beclometasone Dipropionate	Trinity
	Breath actuated (CFC)	AeroBec Autohaler®	3M
		Beclazone Easi-Breathe ®	IVAX
	Breath actuated (HFA)	Qvar Easi-Breathe®	3M
budesonide	pMDI (CFC)	Pulmicort	AstraZeneca
	Dry powder	Budesonide Cyclocaps Cyclohaler®	APS
		Novolizer	Viatris
		Pulmicort Turbohaler®	AstraZeneca
	Nebuliser	Pulmicort Respules®	AstraZeneca
Ciclesonide*	pMDI (HFA)	Alvesco®	Altana
fluticasone propionate	pMDI (HFA)	Flixotide Evohaler®	Allen & Hanburys
	Dry powder	Flixotide Accuhaler®	Allen & Hanburys
		Flixotide Diskhaler ®	Allen & Hanburys
	Nebuliser	Nebules®	Allen & Hanburys

* Not currently licensed in children under 12 years. Possible licence extension in 2006

Combination inhalers

Drug	**Device type**	**Name**	**Manufacturer**
budesonide + formoterol fumarate (Symbicort)	Dry powder	Symbicort Turbohaler®	AstraZeneca
fluticasone propionate + salmeterol (as xinafoate) (Seretide)	pMDI (HFA)	Seretide Evohaler®	Allen & Hanburys
	Dry powder	Seretide Accuhaler®	Allen & Hanburys

From British National Formulary (BNF) 50[6]

pMDI – pressurised metered-dose (aersosol) inhalers
CFC – chlorofluorocarbon propellant; HFA – hydrofluoroalkane propellant

Appendix 9.3 Draft Medline (Ovid) search strategy

Clinical-effectiveness

1 exp asthma/
2 asthma.ti,ab.
3 1 or 2

4 exp randomized controlled trials/
5 exp random allocation/
6 controlled clinical trials/
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 exp double blind method/
10 exp single blind method/
11 (randomiz$ or randomis$).ti,ab.
12 placebo.ti,ab.
13 (singl$ or doubl$ or tripl$ or trebl$ or blind$).ti,ab.
14 (trial$ or study or studies or method$).ti,ab.
15 13 or 14
16 meta analysis/
17 (meta analys?s or metaanalys?s).ab,pt,ti.
18 (systematic$ adj2 (review$ or overview$)).ti,ab.
19 or/16-18
20 or/4-12,15,19
21 (letter or editorial or comment).pt.
22 20 not 21
23 3 and 22
24 beclomethasone/
25 bdp.ti,ab.
26 budesonide/
27 (beclomet?asone or budesonide or ciclesonide or fluticasone or mometasone).mp.
28 (asmabec or belclazone or cyclocaps or becodisks or becotide or filair or qvar or pulvinal or pulmicort or flixotide or aerobec or becloforte or novoliser or viatris or alvesco or asmanex).mp.
29 exp glucocorticoids/
30 (corticosteroid$ or glucocorticoid$ or steriod$).ti,ab.
31 or/24-30
32 31 not 21
33 23 and 32
34 limit 33 to (humans and english language)
35 or/24-28
36 35 not 21
37 23 and 36
38 limit 37 to (humans and english language)

Cost-effectiveness

1 exp Asthma/
2 asthma.ti,ab.
3 1 or 2 (83587)
4 exp ECONOMICS/
5 exp ECONOMICS, HOSPITAL/
6 exp ECONOMICS, PHARMACEUTICAL/
7 exp ECONOMICS, NURSING/
8 exp ECONOMICS, DENTAL/
9 exp ECONOMICS, MEDICAL/
10 exp "Costs and Cost Analysis"/
11 Cost-Benefit Analysis/
12 VALUE OF LIFE/
13 exp MODELS, ECONOMIC/
14 exp FEES/ and CHARGES/
15 exp BUDGETS/

16 (economic$ or price$ or pricing or financ$ or fee$ or pharmacoeconomic$ or pharma economic$).tw. (
17 (cost$ or costly or costing$ or costed).tw.
18 (cost$ adj2 (benefit$ or utilit$ or minim$ or effective$)).tw.
19 (expenditure$ not energy).tw.
20 (value adj2 (money or monetary)).tw.
21 budget$.tw.
22 (economic adj2 burden).tw.
23 "resource use".ti,ab.
24 or/4-22
25 news.pt.
26 letter.pt.
27 editorial.pt.
28 comment.pt.
29 or/25-28
30 24 not 29
31 3 and 30
32 Beclomethasone/
33 budesonide/
34 bdp.ti,ab.
35 (beclometasone or beclomethasone or budesonide or ciclesonide or fluticasone or mometasone).mp.
36 (pulmicort or flixotide or asmanex or novoliser or becotide or asmabec or belclazone or cyclocaps or becodisks or filair or qvar or pulvinal or aerobec or becloforte or viatris or alvesco).mp.
37 32 or 33 or 34 or 35 or 36
38 31 and 37
39 limit 38 to (humans and english language)

Appendix 9.4 Data extraction form (RCTs and systematic reviews)

RCTs

Reviewers:			
Reference	**Intervention**	**Participants**	**Outcome measures**

Reviewers:			
and Design			
RefID: Author: Year: Country: Study design: Number of centres: Funding:	<u>Group A:</u> n = Drug 1 Dose: Duration: <u>Group B:</u> n = Drug 1 Dose: Duration: Add further arms as necessary	Number of Participants: Sample attrition/dropout: Sample crossovers: Inclusion/exclusion criteria for study entry: Characteristics of participants: (e.g. age, gender, previous treatment history, smoking status, co-morbidities,	Primary outcomes: Secondary outcomes: Methods of assessing outcomes: Length of follow-up:

Results			
Outcomes (including patient sub-groups)	**Treatment X (n=)**	**Comparator X (n=)**	**P Value**
Lung function (FEV_1; PEF)			
Symptoms			
Acute exacerbations			
Adverse events			
QoL			
Use of systemic corticosteroids			
Mortality			
Other outcomes			
Comments			

Reviewers:

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups:
- Blinding:
- Comparability of treatment groups:
- Method of data analysis:
- Sample size/power calculation:
- Attrition/drop-out:

General comments

- Generalisability:
- Outcome measures:
- Inter-centre variability:
- Conflict of interests:

Systematic reviews

Reviewers:	
Reference and Design	**Methods**
Author Year Ref ID *Study design:*	Aim (Question): Search strategy: databases searched Inclusion criteria used. *Interventions:* *Comparators:* *Participants:* *Outcome measures:* *Study design:* Quality assessment: Application of methods:
Results (including): • Quantity and quality of included studies. • What was the combined treatment effect? (Should include point estimates and confidence intervals/standard deviations, P values etc for each outcome assessed): • Assessment of heterogeneity:	
Comments: • e.g funding, any other methodological elements that may affect the rigour of the systematic review	

Appendix 9.5 Quality assessment criteria (RCTs and systematic reviews)

a) Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	

From: NHS Centre for Reviews and Dissemination – Undertaking Systematic Reviews of Research on Effectiveness**:** Guidance for those Carrying Out or Commissioning Reviews (Report 4)
http://www.york.ac.uk/inst/crd/report4.htm

b) Quality assessment for systematic reviews, using the NHS CRD DARE criteria

Quality Item	**Yes/No/Uncertain**	**Methodological Comments**
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?		
2. Is there evidence of a substantial effort to search for all relevant research?		
3. Is the validity of included studies adequately assessed?		
4. Is sufficient detail of the individual studies presented?		
5. Are the primary studies summarised appropriately?		