Appendix C

National Institute for Health and Clinical Excellence

Corticosteroids for the treatment of chronic asthma in children under the age of 12 years

Response to consultee and commentator comments on the draft scope

Comments on the draft scope

Section	Consultees		Action
Background information	GlaxoSmithKline	The background on asthma as a disease is succinct and covers the necessary ground. The BTS guidelines have been paraphrased and this makes it difficult to see the difference between the guidelines for children under 5 and those from 5-12. We feel that including the BTS guidelines verbatim rather than paraphrasing would add clarity to the scope.	This would make the scope too lengthy. Added reference to the SIGN web site URL.
	Altana Pharma UK Ltd	We are content with the accuracy and completeness of this information.	No action required
	Trinity-Chiesi Pharmaceuticals Ltd	We are content with the accuracy and completeness of this information.	No action required
	Barts and the London NHS Trust	This should be written by a paediatrician with an up-to date knowledge of the subject of asthma and pre-school wheeze. I have written some observations within the text.	Scopes are written by NICE technical staff.
	British Thoracic Society	You state state British guidelines state that at step 3 "In children aged under 2 years, referral to a respiratory paediatrician should be considered". The BTS/SIGN guidelines do not state this, and do not differentiate between children under 5 and those under 2 years of age; I do not understand where this subdivision has arisen	See figure 6 in full guideline (2005 revision) – at step 3 in children under 2 years the guideline states “consider proceeding to step 4”, step 4 is referral.
	Cochrane Airways Group	Fine	No action required
	Department of Health Child Health branch	The background is I believe correct, but there needs to be greater clarity about actions in younger children. Referral to a respiratory paediatrician (step 2 for children <2, step 3 for children <4) - is there going to be guidance for the respiratory paediatricians receiving these referrals	Younger children will be considered as a subgroup.

Section	Consultees		Action
	General Practice Airways Group	Add the criteria for starting ICS as recommended by SIGN/BTS clinical guidelines	Added
Background information	Glasgow Respiratory Group, University of Glasgow	Minor comment only: Page 2 Spelling, cromones not chromones	Corrected
	Royal College of Nursing	The increase in children being diagnosed with asthma did indeed increase from 60s to 80s but there has now been a decline in the incidence of asthma from 1993, also reflected in reduced numbers of hospital admission. Fleming et al ArchDisChild 2004;89:282-285 Morrison & McLoone Thorax 2001;56:687 -690	Added an additional sentence to reflect declining consultations
		Page 1: Non-asthmatic viral wheeze is misleading terminology. Viral induced asthma may be better wording considering the age group of this appraisal. The use of the word people in the 3rd paragraph should be changed to children in both instances.	Changed
		Page 2: 2nd paragraph. This should be changed to read ….optimisation of respiratory function. (Peak flow is only one measurement that is used in children aged 5 years and over.)	Removed
		Page 2: Step 2. Zafirlukast should be removed as the licence indications are from 12 years of age. Last sentence should read- leukotriene should be considered. (rather than tried).	Removed zafirlukast
		Step 2 'Introduction of regular preventer therapy' aminophylline is mentioned as an additional treatment. This can only be given IV and so should not be included. As chromes are put first in the list of additional therapies does this, subliminally, suggest it should be tried first? We believe it should be last on the list.	Oral preparations of aminophylline are available and licensed for use in children aged 3 years or over. There is no significance to the order of the list – this is in the same order as in the BTS/SIGN guideline.

Section	Consultees		Action
		Page 2 Step 3. Last bullet point. Change to read …should be considered if the diagnosis is in doubt or there is no response to treatment.	Added
	Royal College of Nursing	Re Step 4 ; Slow release beta2 agonist tabs: These are not used in children generally despite them having a license for 3 to 12 year olds. (Obviously young children cannot take tablets) It would be a retrogressive step anyway to embark on oral b2 agonist therapy (even if slow release) because of ineffective route and high risk of side effects such as tachycardia and hyperactivity. BTS/SIGN do not include them in the guidelines.	Removed
	Royal College of Paediatrics and Child Health	General: This should be written by a paediatrician with an up-to date knowledge of the subject of asthma and pre-school wheeze. I have written some observations within the text. It would be helpful to have some comment on the concerns about adverse effects of inhaled steroids. Paragraph 1, last sentence: Some experts have reservations about this, particularly PEF. Sensitivity to aeroallergens has a better diagnostic profile	Scopes are written by NICE technical staff. Reference to PEF removed
The technology/ intervention	GlaxoSmithKline	Further consideration should also be given to the introduction of CFC-free inhalers, not only in terms of the environment but also in terms of which products will actually be available for prescribers in the future.	Noted
	Altana Pharma UK Ltd	We are content that the description of the technology is accurate.	No action required
	AstraZeneca UK Ltd	To follow current English/Welsh terminology, AstraZeneca suggest substitution of the phrase ‘compound preparations’ with ‘combination inhalers’ to indicate use of an inhaled corticosteroid and long acting beta agonist in the same inhaler.	Changed
	Trinity-Chiesi Pharmaceuticals Ltd	We are content that the description of the technology is accurate	No action required

Section	Consultees		Action
The technology/ intervention	VIATRIS Pharmaceuticals Ltd	The description of the three inhaled corticosteroids for use in children is accurate, but the list of technologies is confusing and does not appear to be complete. Viatris would recommend reviewing this list carefully before the scope is finalised. Specifically the Viatris product is incorrectly named. The correct name is 'Novolizer Budesonide' please note the 'z'. Novolizer is the brand name for the inhaler device. In addition, the list of beclometasone technologies is not comprehensive. In order to simplify the list of technologies Viatris would recommend that the technolgy list is separated into 2 sublists, i.e i) inhaled corticosteroids and the combinations , ii) delivery systems	Corrected spelling Added one additional beclometasone product – not aware of any others (based on British National Formulary).
	Barts and the London NHS Trust	Yes *(In answer to the question "Is the standard description of the technology accurate?")*	No action required
	Cochrane Airways Group	Yes - see concerns with regard to adults	No action required
	General Practice Airways Group	Yes It would be useful to consider the behaviour of a drug administered by a spacer device since this is common in children.	Devices considered in previous appraisal – this appraisal will concentrate on differences between drugs.

Section	Consultees		Action
The technology/ intervention	Royal College of Nursing	Need to include the beclometasone Easyhaler. Budesonide is also imminent in this device. Qvar (HFA Bdp) should be excluded it is licensed for 12 yrs and above only. Licence for younger children was declined. Cyclocaps device - rarely used in paediatrics -individual capsule device, better devices available. Paucity of evidence available. However recognise appraisal must be inclusive. Compare formulations in like devices whenever possible but acknowledge differences bewteen devices if this is not possible Beclometasone is not available in a nebulisation formulation, just budesonide and fluticasone are. In the section on Compound preparations , the lowest dose of Seretide should be added in brackets as it has been for Symbicort. Ciclesonide (AltanaPharma) is a once daily inhaled steroid, licensed for 18 yrs and above at moment but ultimate aim will be down to 6 and above. Paediatric license is fairly imminent. It is a novel pro-drug. Should we not consider this drug also?	Easyhaler added QVAR removed. Beclometasone nebuliser suspension removed. Have deleted dose for Symbicort rather than adding for Serevent – the dose for Serevent differs between formulations and this would make the sentence unwieldy. Ciclesonide added
	Royal College of Paediatrics and Child Health	The recommended method for administration of these drugs is by MDI and large volume spacer device. However, there are a number of different spacer devices and their performance will need to be taken into account to make meaningful comparisons.	This is not specifically a comparison of devices
	Royal College of General Practitioners	Yes *(In answer to the question "Is the standard description of the technology accurate?")*	No action required
Licensing issues	Altana Pharma UK	In confidence information removed	
	AstraZeneca UK Ltd	In confidence information removed	

Section	Consultees		Action
Licensing issues	GlaxoSmithKline	No current licence updates for GSK technologies Becotide, Flixotide or Seretide are due for this age group in the timescale of this review.	No action required
	Trinity-Chiesi Pharmaceuticals Ltd	In confidence information removed Pulvinal was licensed in January 2001.	
	VIATRIS Pharmaceuticals Ltd	Detailed in separate document In confidence information removed	
Population	GlaxoSmithKline	The suggested populations seem reasonable, although it may be more appropriate to follow the two BTS guidelines for children aged 5-12 and children aged 5 and under.	Age subgroups were discussed and agreed at scoping workshop in December 2004
	Altana Pharma UK Ltd	In our opinion the population is defined appropriately and there is no need to consider other populations separately.	No action required
	AstraZeneca UK Ltd	AstraZeneca would suggest clarification at this stage that the relevant population are those children younger than 12 years with chronic asthma.	Added the word chronic
	Trinity-Chiesi Pharmaceuticals Ltd	In our opinion the population is defined appropriately and there is no need to consider other populations separately.	No action required
	Barts and the London NHS Trust	This is the most important part: atopic and non-atopic patients need to be assessed seperately. Their disease and its progression are quite different although there is of course some patients with overlap.	Added something in other considerations regarding possible subgroups

Section	Consultees		Action
Population	British Thoracic Society	You state: Children younger than 12 years with asthma. The following subgroups should be considered • Children younger than 2 years • Children between the ages of 2 and 4 years • Children between the ages of 5 and 11 years" Given that the BTS/SIGn guideline does not distinguish between children <2 and those <5 in either the diagnosis or pharmacological treatment sections, I think it will be difficult to ensure consistency between the two documents if the NICE document attempts to do so. There is very little, if any, published data on pharmacological management specifically in the under 2s, and alll of the studies of which I am aware use "preschool" ie <~5years as inclusion criteria. Whilst there are some differences in the diagnositc and therapeutic approach between children <2 and those 2-5, we a re dealing with a continuum and I would suggest that it would be best to stick simply to looking at <5s as a single group.	This subdivision was discussed and agreed at the scoping workshop in December 2004.
	Cochrane Airways Group	5-12s are acceptable for the purposes of diagnosing asthma, although do bear in mind that many young children struggle to undertake spirometry and so in the younger range of ages, different outcomes may be more acceptable - e.g. exacerbations, requirement for rescue medication usage and symptoms, rather than spirometry.	Reference to PEF removed
	Department of Health Child Health branch	The younger child, including the infant	This population is included
	General Practice Airways Group	Yes *(In answer to the question "is the population defined appropriately?")*	No action required
	Royal College of Nursing	Should match the age groups specified in the BTS/SIGN asthma guideline. Very important to look at under 2's as a separate age group, as well as the other age group divisions	No action required

Section	Consultees		Action
Population	Royal College of General Practitioners	Need also to look at specific needs of children with disabilities (including hearing, deafness, learning) and ethnic diversity.	It is unclear how disabilities and ethnic diversity will affect response to different drugs. (NB this is not an appraisal comparing devices)
	Royal College of Paediatrics and Child Health	This is the most important part: atopic and non-atopic patients need to be assessed seperately. Their disease and its progression are quite different although there is of course some patients with overlap.	Added something in other considerations regarding possible subgroups
	Southampton Health Technology Assessments Centre (SHTAC) and Peninsula Technology Assessment Group (PenTAG)	The population should be defined as having 'chronic asthma' to be consistent throughout the scope	Added the word chronic
Comparators	GlaxoSmithKline	The appraisal objective is to appraise the clinical and cost effectiveness of corticosteroids which would meet the criteria of an appraisal. The current scope appears to cover a broader remit and wider comparisons. Firstly, the scope appears to be addressing alternative treatment management strategies by making comparisons between compound products and increased dose ICS and compound products with the addition of oral bronchodilators. This would appear to make the review more like a clinical guideline. (As a point of clarification, the scope should also specify whether ICS will be compared only when used alone or when used in combination with LABAs) Secondly, this broader approach means that the review will be inordinately complex due to the extensive number of comparisons it would require to be made.	The number of comparators have been minimised as far as possible in order to facilitate this complex appraisal. Corticosteroids will be compared with each other regardless of concomitant therapy. Combinations will be compared with corticosteroids alone and the use of two separate inhalers (one corticosteroid and one LABA).

Section	Consultees		Action
Comparators	GlaxoSmithKline	This complexity and broad remit lead us towards a view that this is best served either as a guideline or alternatively as a specific appraisal of ICS within a broader clinical guideline process. In answer to the specific questions for consultation, we do not feel it is appropriate to compare the compounds with combinations of ICS and oral bronchodilators, nor to increased dose of ICS or to make broader comparisons with the use of cromones and leukotriene receptor antagonists (LTRAs). We believe this would make the review unfeasible and is beyond the stated appraisal objectives. To limit the review to comparisons of ICS alone, ICS in combination with LABA, or the use of compound products will result in a more meaningful appraisal whilst still addressing the original remit.	Would there be added value in another clinical guideline given the existence and established status of the BTS/SIGN document?
		We agree that this appraisal should follow the stepwise approach recommended in the BTS guidelines. However, further specifying which comparisons should be made at clinically relevant dose equivalents at each BTS step would clarify the appraisal. We also recognise that dose equivalence should be taken into account when defining appropriate comparisons. However, it is also important to retain a degree of pragmatism to take account of realistic therapeutic alternatives. The ages at which ICS are licensed for children vary significantly and it would be of benefit to specify which ICS would be compared within each age group.	This may overcomplicate the scope – would expect this to be addressed by the assessment group.
	Altana Pharma UK	In our opinion, yes. *(In answer to the question "Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared?")*	No action required
	AstraZeneca UK Ltd	Inhaled corticosteroids For nebulised preparations, particularly for the paediatric population, the comparator is often not an active comparator but placebo. To ensure that valuable data are not 'lost' when NICE conducts its review, where no substantial data exist the Institute should accept placebo as a valid comparator.	Placebo is not a relevant comparator for the purposes of this appraisal

Section	Consultees		Action
Comparators	AstraZeneca UK Ltd	Compound preparations (Combination preparations) The mainstay of paediatric asthma treatment within England and Wales constitutes use of inhaled corticosteroid and short/long acting bronchodilator. National guidelines (e.g. BTS Guidelines) endorse this approach and as such, use of other agents such as LTRAs, theophyllines, cromones etc is very limited. There are very limited data available to inform on effectiveness. Therefore to ensure guidance produced is the most relevant possible, AstraZeneca would strongly suggest that inhaled corticosteroids in combination with cromones, theophyllines, LTRAs etc are not standard comparators in clinical practice and should be removed from the appraisal of compound inhalers.	It has been decided to limit comparators to a minimum to facilitate this complex appraisal. Leukotriene antagonists, theophyllines and cromones will not be comparators
	Merck Sharp & Dohme Ltd. (MSD)	We support the inclusion of other treatments for asthma in combination with inhaled corticosteroids as comparators. If comparisons are to be made with other treatments not in combination with inhaled corticosteroids ie as first-line monotherapies, then the Institute should be mindful that there are conflicts between the licenced indications of some treatments and the recommendations made by some learned societies (such as the British Thoracic Society) regarding their use in children which will pose a dilemma to the prescriber; accordingly, it would be proper for NICE to advise prescribers as to how to address this conflict, mindful of the implications of prescribing outside of the licenced indications . Problems with administration also need to be addressed.	It has been decided to limit comparators to a minimum to facilitate this complex appraisal. Leukotriene antagonists will not be comparators.
	Trinity-Chiesi Pharmaceuticals Ltd	In our opinion, yes. *(In answer to the question "Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared?")*	No action required

Section	Consultees		Action
Comparators	VIATRIS Pharmaceuticals Ltd	What is meant by the term 'agent'? Does this mean the "pharmcologically active agent' or 'the pharmacologically active agent and the delivery system'? It will not be possible to compare the corticosteroids given via different dry-powder inhalers because there is no DPI that incoporates more than one of the corticosteroids to be compared. Alternatively, the different corticosteroid treatments could be compared using pMDIs to establish the pharmacoligical effectiveness and relevance of the molecules for the treatment of asthma. Following this a comparison of different inhalers with the same corticosteroid e.g. budesonide which can be delivered by the Turbohaler® and the Novolizer® and beclametasone which can be delivered by a variety of inhaler devices. This could help to establish the comparative, efficacy and cost-effectiveness of the different products. If analysed in this way the guidance may make one level of conclusions regarding the choice of corticosteroid and a second level of conclusions regarding the choice of delivery systems. The combinations could be compared in the same way. This is perhaps long-winded, but is reflective of the complexity of the comparisons needed.	Agent changed to drug Indirect comparisons are possible Methods of analysis will be determined by the Assessment Group.
	Asthma and Allergy research Group, University of Dundee	Should be comparison of ICS +LABA vs ICS +LTRA or ICS +Theophylline	It has been decided to limit comparators to a minimum to facilitate this complex appraisal. Leukotriene antagonists and theophyllines will not be comparators.
	General Practice Airways Group	Yes - but all add-on options including LTRAs and cromones should be considered	It has been decided to limit comparators to a minimum to facilitate this complex appraisal. Leukotriene antagonists and cromones will not be comparators.
	Cochrane Airways Group	Yes - dose ranges are important to consider in children.	No action required

Section	Consultees		Action
Comparators	Department of Health Child Health branch	no mention of atrovent	Classed as a short acting bronchodilator by BTS and only mentioned at step 1. Not considered as comparators at the relevant later steps in the guideline
	Royal College of Nursing	Inhaled corticosteroids (ICS)- the appropriateness of the device must be considered as well in this age group, because of difficulties of using some devices and acceptability of others. There are 3 groups of devices: metered dose inhaler +/- spacer and +/- face mask according to age; dry powder device and breath actuated device. While we recognise that this appraisal is about drugs rather than devices, in the under 12's they should not be separated. The 5-15 year old NICE inhaler appraisal recognises the importance of the device. Different inspiratory effort is also needed for different devices. Equally disease severity will affect drug deposition in the lungs. The appraisal should compare each ICS through the same inhaler device, whenever possible. Re compound preparations: ICS and LABA (long acting bronchodilator) separately and in combination - evidence is limited in this age group. Increased ICS dose - Why? Guideline evidence has already looked at this and must be referred to. We think this is a duplication of effort when a robust review of the evidence has already taken place following SIGN appraisal guidelines. ICS + other drugs- again why? See comments above. Not sure about using cromones as a comparator. ?Bronchodilator usage, though this is linked obviously with symptoms	It is acknowledged that drug and device cannot be separated. The BTS/SIGN guideline did not consider cost effectiveness so this is not duplication of effort.
	Royal College of General Practitioners	Yes but all add-on options including LTRAs and chromones should be considered. Consideration should be given to factoring in comparison of the different delivery systems especially with regard to each age group	It has been decided to limit comparators to a minimum to facilitate this complex appraisal. Leukotriene antagonists and cromones will not be comparators

Section	Consultees		Action
Comparators	Royal College of Physicians of Edinburgh	Should be comparison of ICS +LABA vs ICS +LTRA or ICS +Theophylline.	It has been decided to limit comparators to a minimum to facilitate this complex appraisal. Leukotriene antagonists and theophyllines will not be comparators
	SHTAC and PenTAG	In relation to compound preparations containing a corticosteroid and a long-acting beta2 agonist for inhalation compared to inhaled corticosteroids and long-acting beta2 agonists administered by separate inhalers - the advantage of compound preparations appears to be convenience for the patient who only has to use (and carry with them) one inhaler instead of two. However, there may be little difference in clinical and cost effectiveness between these two modes of delivery, assuming little or no difference in cost or efficacy. This may not, therefore, be a useful comparison.	Have now limited this comparison to the economic analysis only – i.e. a comparison of the costs of the different means of administration assuming equivalence in effectiveness.
Outcomes	GlaxoSmithKline	The appraisal does need to cover a range of outcomes, as it is now well recognised that patient reported outcome measures are as important as objective lung function measures and they enable a consideration of the total impact of asthma on the patient. In addition, due to the length of time over which ICS have been researched, the outcome measures can vary significantly between trials. Therefore, when making comparisons, the outcome measures must not only be meaningful clinical measures of asthma but also standard so that cross trial comparisons are valid.	Patient reported outcomes will be measured in the assessment of health-related quality of life.
		From our experience in the asthma research field, we would suggest that as a minimum, the most appropriate measures of lung function are: FEV1 and change in morning PEF.	FEV_1 and PEF included already
		In terms of symptoms, the variation in the ways in which ‘wheeze’ and ‘shortness of breath’ can be measured will be hugely variable across studies, if measured at all. We would suggest that symptom free days and symptom free nights would be more meaningful, comparable and universal measures for symptoms, in addition to use of relief medication.	Symptom-free days/nights added

Section	Consultees		Action
Outcomes	GlaxoSmithKline	Exacerbations need to be clearly defined, as these can range from a small change in medication to hospitalisation. For HR QOL, consideration of appropriate tools for generating utility data for the age in question needs to be made.	Added acute mild and acute severe definitions as suggested below. In general, scopes do not recommend one tool or measurement scale over another for any outcome. The difficulties of generating utility data in children have been encountered in several appraisals and are acknowledged.
	Altana Pharma UK	In our opinion, yes. *(In answer to the question "Will these outcome measures capture the most important health related benefits of the technology?")*	No action required
	AstraZeneca UK Ltd	AstraZeneca believe it is important that the term 'acute exacerbations' is defined within the scope. We believe it should be split into 'acute mild' and 'acute severe' exacerbations and that the definitions of these are as follows: ¨ Acute mild = contact with healthcare professional required ¨ Acute severe = hospitalisation, course of oral steroids or visit to A+E required AstraZeneca also believe that there should be a separate outcome based on reliever use only. This is because reliever use is a standard outcome that is measured in the majority of clinical trials conducted in asthma.	Added Not added – it is difficult to relate the use of as required medication to clinical outcome
	Trinity-Chiesi Pharmaceuticals Ltd	In our opinion, yes. *(In answer to the question "Will these outcome measures capture the most important health related benefits of the technology?")*	No action required

Section	Consultees		Action
Outcomes	VIATRIS Pharmaceuticals Ltd	Other outcomes that could be considered: - waking at night, - Interference with daily physical activity. - hospitalisations. Unless the use of systemic corticosteroids is a marker for hospitalisations, we would recommend the 'number of non-routine hospitalisations' as an outcome measure as this will dramatically affect the cost-effectiveness of a treatment. - compliance. This is particularly important in ensuring asthma control with corticosteroids. The BTS/SIGN guidelines recommend the checking of compliance before escalating to step 3.	Added symptom-free nights as an outcome and hospitalisation forms part of the definition of a severe exacerbation. Interference with physical activity should come out in health-related quality of life measurements. Compliance is an issue for most drug-related appraisals but data are often poor or absent.
	Asthma and Allergy research Group, University of Dundee	Should include surrogate inflammatory markers such as airway hyperreactivity, exhaled nitric oxide, sputum eosinophils, serum ECP, markers of airway remodelling Need to evalaute exacerbations not just in terms of % reduction but also in terms of NNT from meta-analysis	Do not usually include surrogate markers if clinical outcome data are available.
	Barts and the London NHS Trust	For groups yes but when the outcomes are related to individuals the problem of diagnosis and severity return. Treatment adherence is the biggest issue in the clinical arena.	Treatment adherence is always an issue with appraisals of drug treatments, but good data are often lacking.
	Cochrane Airways Group	What is considered an important change may well differ from child to child (not least due to age and severity). % predicted (i.e. reference scales) for lung function and growth rates would be useful for these reasons	For consideration by assessment group protocol
	General Practice Airways Group	Would recommend including primary care consultation rate and secondary care hospitalisation and A+E attendance also. It will be important to encompass 'real-world' issues such as compliance and inhaler technique in the evaluations and to recognise that generalisability from RCTs may be an issue. Observational studies should be included in the analysis of evidence	This may be captured by new definition of exacerbation. Assessment group will determine methodological inclusion criteria.

Section	Consultees		Action
Outcomes	Royal College of General Practitioners	Would recommend including: 1) primary care consultation rate, secodary care hospitalisation and A+E attendance and school attendance/other psychosocial outcomes as well. 2) encompass 'real-world' issues such as compliance and inhaler technique in the evaluations and to recognise that generlisability from RCTs may be an issue. Observational studies should be inckuded in the analysis of evidence 3) How does the potency of inhaled steroids compare? 4) What effect does delivery system make? 5) How do the relative side effect profiles compare? 6) What are the clinical and cost implications of using combination products? 7) Are there quality issues with generic pMDIs?	1) may be captured by new definition of exacerbation. Potency and device related issues will have to be taken into account as far as the evidence allows. Quality of licensed products is not within the Institute's remit.
	Royal College of Paediatrics and Child Health	For groups yes but when the outcomes are related to individuals the problem of diagnosis and severity return. Treatment adherence is the biggest issue in the clinical arena.	Treatment adherence is always an issue with appraisals of drug treatments, but good data are often lacking.
	Royal College of Physicians of Edinburgh	Should include surrogate inflammatory markers such as airway hyperreactivity,exhaled nitric oxide ,sputum eosinophils , serum ECP,markers of airway remodelling. Need to evalaute exacerbations not just in terms of % reduction but also in terms of NNT from meta-analysis.	Do not usually include surrogate markers if clinical outcome data are available.

Section	Consultees		Action
Outcomes	Royal College of Nursing	Objective measures of lung function - age must be included here as in the younger child technique is variable. Tests must be repeatably reliable to be relevant. They cannot be used in isolation but in association with symptoms. Incidence of acute exacerbation- include hospital admission and whether life threatening etc as per the BTS/sign guidelines (see Appendix charts). outcome section question: Agree that all of the outcomes specified are relevant for the appraisal. However Does the 'health related quality of life outcome' need to include the specific quality of life indicators to be measures e.g difficulty sleeping, interference with daily activities etc. Does the appraisal also need to include and outline the specific tool that will be used to measure health related quality of life for example the rcp three questions or juniper quality of life tool.	The acute exacerbation outcome has been clarified It is not usual to specify quality of life measurement scales in the scope – will be determined by the evidence available.
Economic analysis	GlaxoSmithKline	Due to the large number of potential comparisons, the economic analysis will be necessarily complex and extensive. In addition to the number of clinical comparisons to be made, the pricing structure of these medications means that a further number of comparisons would be needed when costs of medications are taken into account. There are a number of technical issues where a more detailed discussion between the assessment groups and manufacturers may reduce uncertainty. For example, as most ICS come in a variety of preparations, they can be used in many combinations to reach a required dose. A potential approach of price per 100mcg (per BDP equivalents) for each product weighted by its use in practice could be followed to allow for simpler comparisons. In addition consideration will be needed of the appropriate approach to generate utility data in children. Whilst issues such as this may not strictly be a scoping issue, an agreed approach may allow more meaningful submissions to be made.	Noted Noted Noted The Assessment Group's protocol will address methodological issues. The difficulties of generating utility data in children have been encountered in several appraisals and are acknowledged.

Section	Consultees		Action
Economic analysis	General Practice Airways Group	The literature often quotes cost per asthma-free or symptom -free day.	A NICE appraisal requires preference-based utilities where possible.
	Asthma and Allergy research Group, University of Dundee	Time off school is key outcome in kids	May be difficult to assess the consequences of this.
	Royal College of Nursing	Appropriate if looking at cost but are there any other economic measures that could be looked at for example preventing hospital admission, number of school days lost as a result of asthma, parents not taking time out of work to care for children with symptomatic asthma etc	Perspective is as stated in the methods guide
	Royal College of Physicians of Edinburgh	Time off school is key outcome in kids.	May be difficult to assess the consequences of this.
	Royal College of Paediatrics and Child Health	I would be inclined to look at the benefit ALL children prescribed ICS obtain. This would give a more realistic picture of what really is going on.	
Other considerations	GlaxoSmithKline	The initial searches within GSK indicate that from GSK sponsored studies alone we have a large number of studies that may be relevant. Obviously, broader literature searches will generate even more studies for consideration. The quality and relevance of all these studies will be variable, and there is a tendency for asthma studies to be unblinded. Thus when combining trial data, particular consideration should be given to the evidence hierarchy.	Noted The Assessment group will determine the inclusion criteria, quality assessment, and the methods for combining data
	AstraZeneca UK Ltd	These questions have been covered within the discussions above (please see comparator section).	
	Trinity-Chiesi Pharmaceuticals Ltd	Will consideration be made of CFC-formulations and if so will they be compared to non-CFC-free agents?	This is not a comparison of formulations – non-equivalence of devices will be taken into account as far as possible.

Section	Consultees		Action
Other considerations	VIATRIS Pharmaceuticals Ltd	This review does not cover delivery systems specifically. However, as stated below recently there have been technological advances in dry powder inhalers. The last NICE review for the use of inhalers in children was conducted in 2000 and no further review is planned. Therefore, it could be of use to compare some of the basic properties of the inhalers in this review perhaps covering lung deposition, inhaler internal resistance, ease-of-use, patient compliance etc.	Effectiveness is determined both by the pharmacological agent and by the delivery system. General advice on inhalers is outside the remit.
	Asthma and Allergy research Group, University of Dundee	Allergic rhinitis and its impact on asthma -eg adding LTRA may treat upper and lower airway inflammation in allergic asthma and concomitant rhinits .Effect of intranasal steroid on asthma exacerbations	Outside remit (not appraising LTRAs)
	Cochrane Airways Group	Will there be an attempt to describe the methods to be used in how evidence will be assessed? What use will be made of existing reviews of evidence? How will it be graded/scrutinised? How will unpublished evidence be used?	This will be addressed in the Assessment Group's protocol for their review.
	General Practice Airways Group	The varying dose response (using different outcome measures) of different ICS should be considered.	In so far as the evidence allows
	Glasgow Respiratory Group, University of Glasgow	Subgroups: consider smokers with asthma compared to never & ex-smokers with asthma	Relevant to this age group?

Section	Consultees		Action
Other considerations	Royal College of General Practitioners	The Welsh Assembly Government is mentioned – in Wales we have an independent Children's Commissioner, should his office be included?	The Welsh Assembly Government will be invited to participate as a 'consultee' . Welsh professional and patient organisation's will be invited to participate as 'commentators', along with the National Public Health Service for Wales and the Board of Community Health Councils in Wales
	Royal College of Paediatrics and Child Health	Treatment adherence	An issue for most drug-related appraisals but data are often poor or absent.
	Royal College of Physicians of Edinburgh	Allergic rhinitis and its impact on asthma -eg adding LTRA may treat upper and lower airway inflammation in allergic asthma and concomitant rhinits .Effect of intranasal steroid on asthma exacerbations.	Outside remit (not appraising LTRAs)
	Royal College of Nursing	Essential that the BTS/SIGN guidelines are referred to in the appraisal. Agree that ICS should normally only be appraised in accordance with licence indications. However fluticasone often used outside licence age group (ie under 4 years of age) so perhaps this should be considered in view of published evidence of concerns re systemic effects especially with high doses of all ICS. Whilst cost is key, in children under 12 usability and appearance of inhalers is a crucial part of their acceptabilty and therefore impacts hugely on compliance. Would be useful to address this if possible, may not be practicable.	Will not consider outside licensed indication.

Section	Consultees		Action
Additional comments on the draft scope.	GlaxoSmithKline	We strongly believe that the breadth of this review as outlined in the current scope indicates that it should be a guideline and not an health technology appraisal. We believe the potential number of comparisons needed to be made with the scope as it currently stands, make it inordinately complex as an health technology appraisal. We believe that the scope needs to be clarified to focus on the differences between inhaled corticosteroids, as stated in the original remit, rather than considering management strategies. Even this more targeted approach will still involve a large number of comparisons and volume of data.	Would there be added value in another clinical guideline given the existence and established status of the BTS/SIGN document?
	AstraZeneca UK Ltd	As individual inhaled corticosteroids are, by definition, associated with different devices, running double blind studies in the respiratory area is extremely difficult. As such, the majority of clinical trials have been conducted in an open fashion. Additionally, for older inhaled corticosteroids placebo was accepted as a valid comparator. AstraZeneca suggest that restricting inclusion of trials to only those conducted as double blind, active comparator RCTs would result in the bulk of the data on inhaled corticosteroids being excluded, perhaps resulting in inappropriate findings. AstraZeneca suggest that in this instance the Institute takes a pragmatic approach and includes open / placebo controlled studies with an appreciation of the bias that is inherent to these studies compared with double blind active comparator RCTs. We would ask for notice regarding the approach that the Institute envisages taking to ensure that we can prepare the most appropriate submission possible.	Methodological inclusion criteria will be determined by the Assessment Group.
Additional comments on the draft scope.	Merck Sharp & Dohme Ltd. (MSD)	MSD would like to make the following points at this stage in the appraisal process: 1. The problems of administration and compliance regarding inhaled corticosteroids need to be addressed, especially with regards to children. These can result from issues such as children finding the inhalers difficult to use, especially the very young, and parental unease at administering long-term courses of steroids to young children.	Noted This is not specifically comparison of devices.

Section	Consultees		Action
		2. The adverse effects of inhaled corticosteroids on children should be taken into account, including the effects on linear growth and adrenal gland function.	Linear growth added.
		3. We feel that children patients not responding, or responding weakly, to inhaled corticosteroids should not have their dosages titrated up without careful consideration being given to adding in a complimentary treatment within the terms of its licence.	A technology appraisal does not specify the treatment pathway as in a guideline
		4. Inhaled corticosteroids should be compared directly to other interventions for asthma, within the terms of their respective licenced indications. We feel that inhaled corticosteroids are so widely used that NICE guidance should put them in the context of other treatments for asthma in order to be of the most use to health professionals.	It has been decided to limit comparators to a minimum to facilitate this complex appraisal. Leukotriene antagonists will not be comparators
Additional comments on the draft scope.	VIATRIS Pharmaceuticals Ltd	It is noted that this Comments Form does not allow comments on the objective of this appraisal. The objective covers the clinical and cost-effectiveness of corticosteroids in the treatment of asthma. However, recently there have been technological advances in dry powder inhalers resulting in improved lung deposition, compliance and 'ease of use' to the extent that dry powder inhalers may now provide clinical advantage and cost effectiveness over the use of pMDIs. Lung deposition and compliance are key to controlling inflammation and therefore minimising acute episodes and the need for add-on therapy, further intervention such as systemic corticosteroids, or expensive hospitalisations, for example. The delivery system (which may be a dry-powder inhaler) is key in the effectiveness of these corticosteroids. Therefore, it is no longer possible to compare the active agent without the delivery system. Indeed, the NICE draft scope of this review mentions the inhaler technologies (Appendix A; page 3). As the effectiveness and cost effectiveness of the corticosteroids will be influenced by the delivery system Viatris would recommend that the objective of this review should should also cover a review of the delivery system i.e "To appraise the clinical cost effectiveness of corticsteroids and the delivery systems, ..."	The objective for this appraisal is set by the Department of Health and Welsh Assembly Government remit. This is not specifically comparison of devices – it is acknowledged that effectiveness is determined both by the drug and the delivery system

Section	Consultees		Action
Additional comments on the draft scope.	VIATRIS Pharmaceuticals Ltd	Comments on the questions for consultation: Would it be appropriate to make broader comparisons with other drugs such as cromones and leukotriene receptor antagonists? Such comparisons would require broadening this already complex review. It would no longer be a review of corticosteroids, but instead a review of the treatment of chronic asthma.	It has been decided to limit comparators to a minimum to facilitate this complex appraisal.
	General Practice Airways Group	Re questions: We think comparisons of ICS with other drugs are useful.	It has been decided to limit comparators to a minimum to facilitate this complex appraisal.
	Glasgow Respiratory Group, University of Glasgow	1. Not necessary to compare compound preparations with combination of inhaled ICS and oral bronchodilators 2. Appropriate to make broader comparisons with other drugs such as cromones & leukotriene receptor antagonists	It has been decided to limit comparators to a minimum to facilitate this complex appraisal. Cromones and leukotriene antagonists will not be comparators
	Royal College of General Practioners	Re questions: comparisons of ICS with other drugs is useful.	It has been decided to limit comparators to a minimum to facilitate this complex appraisal.
	Royal College of Nursing	Should Altana's ciclesonide be included as they do not yet have a paediatric licence but are seeking it with the MHRA? Novolizer- spelling incorrect in document - z not s Cromoglicate MDI withdrawn by manufacturer. Only Easibreathe and spinhaler devices available.	Ciclesonide included Spelling corrected the scope does not refer to formulations of cromoglycate
	Royal College Of Paediatrics And Child Health	I think a lot of time could be spent on this without considering the real question which for me would be: why are children without asthma and without asthma at Step 2 of the guidelines being prescribed asthma treatment, in particular ICS? You would then see how much money is being spent and wasted on these drugs.	This question is outside the remit of a technology appraisal

The following consultees/commentators indicated that they had no comments on the draft scope

3M Health Care Ltd.
Welsh Assesmbly Government