NICE HTA – Corticosteroids for the treatment of chronic asthma (in children)

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Document. Inhaled corticosteroids and long acting beta agonists in children – Final Protocol	**Section number** Indicate **section number** or **<u>'general'</u>** if your comment relates to the whole document	**COMMENTS** **Please insert each new comment in a new row.**
	General	There are fundamental problems with this NICE document, particularly with regard to the flawed search strategies used and the adult perspective of the document. These criticisms are detailed below as both further general and specific comments.
	General	The background to the document is written from an adult perspective and this pervades and weakens the whole document. This is a fundamental flaw which will weaken its credibility to clinicians and usefulness in practice. It is also not helpful to send out documents for consultation and then send a revised document several weeks later.
	General	Many drugs in paediatric practice are used in unlicensed indications or used off licence. There is a British National Formulary for Children (bnfc.org) and this NICE document which limits discussion only to drugs which are licensed for the indications discussed is of little practical use for the management of asthma in children.
	General	In this and other areas (eg the aims of treatment) the SIGN/BTS guideline, which is also regularly updated as a 'living' guideline, is much more helpful.
	General	The stated aim of this NICE assessment is to assess the clinical effectiveness of ICS (alone), and ICS + LABA in children with chronic asthma. Yet the search strategy does not seem to include studies where the comparator is a placebo. Such studies are essential to this assessment. We would suggest that the whole scoping document needs to be very carefully rethought and a decision made as to whether this review is focused on: (i) the effectiveness and cost effectiveness of the drugs (ICS,

		LABA, and their combination) **or** (ii) whether it is about comparing drugs and strategies, taking the fact that ICS are the most effective and cost effective strategy in children as a given.
	General	In children, in particular, it is imperative to consider the influence of delivery systems for different age groups - eg metered dose inhaler +/- spacers, breath actuated metered dose inhalers, dry powder inhalers and nebulised – as this will determine fine particle dose and systemic adverse effects of inhaled steroids - ie the benefit/risk balance. Under the blanket term of 'spacer devices' there are potential serious confounders. Large volume spacers and small volume spacers for the same sized child will deliver different doses of inhaled steroid to the airway. Clean or (especially new) large or small volume spacers may deliver very much less inhaled steroid than older 'dirtier' devices which have a much reduced static charge on the walls of the device and so retain very much less drug within the spacer. This needs to be considered when reviewing evidence on dose administered. In addition, the dose received may differ greatly from the nominal dose inhaled depending on the physical characteristics of the inhaler, inhaler technique, co-operative state of the child etc.
	General	The remit should have included Montelukast in this important age group, particularly in terms of the cost effectiveness analysis that will ensue.
	4.1	This background is written from an adult perspective. We note this was also commented on in the draft comments. It is not completely relevant to asthma and wheeze as occurring in children. In fact, this adult perspective pervades the whole document eg lung function as an outcome is not relevant for children under 5 years the age where asthma is most common.
	4.2	Most clinicians would include preventing asthma exacerbations as a specific aim. At present, it is only implied in the aim of minimising the need for rescue treatment. There is also no specific comment about physical activity and the need to avoid/minimise limitations. The aims of treatment are better summarised in the introduction to S4 of the BTS SIGN guidelines.
	4.2 page 4	In children 5-12 years, if response remains poor oral corticosteroids can be started but the child <u>should</u> be referred to a specialist paediatrician.
	4.2.1	One of the practical problems paediatricians face is that they are often using these drugs “off licence”. Fluticasone at high doses is an obvious example. Accordingly, guidance about drugs within licence has limitations for paediatric practice.
	5.2.1	Studies of say 4-8 weeks still represent a very short time scale, especially if the aim is to concentrate on clinical effectiveness and

		not just efficacy. A longer duration (say 3 months) for inclusion would seem more appropriate.
	5.2.2	The stated aim of this NICE assessment is to assess the clinical effectiveness of ICS (alone), and ICS + LABA in children with chronic asthma. Yet the search strategy does not seem to include studies where the comparator is a placebo. Surely such studies are essential to this assessment. This was raised by Astra Zeneca in comments on the draft scope. The response was that "placebo is not a relevant comparator for the purposes of this appraisal". However, this response is not consistent with the title or stated aim in section 4. This would suggest that the whole scoping document needs to be very carefully rethought. It needs to be decided whether this review is focused on: (i) the effectiveness and cost effectiveness of the drugs (ICS, laba, and their combination) **or** (ii) whether it is about comparing drugs and strategies taking the fact that ICS are the most effective and cost effective strategy in children as a given. Although many of the comments from the drug industry on the draft scope represent attempts to ensure that their particular products are presented in the best light, some of these tensions about the purpose of the review are reflected in their responses – see, for example, the additional comments from GSK.
	5.2.3	While accepting that evidence about some issues is still accumulating, it would seem reasonable that only studies already published in peer review journals would be appropriate for this assessment. After all, ICS have now been in use for over thirty years in children.
	5.2.4	The target population is children under 12 years with **chronic** asthma. It is not made clear how chronic asthma is defined. Paediatricians would distinguish those with persistent interval symptoms who will often also be atopic from those with viral related wheezing with no interval symptoms. These children are likely to have different responses to inhaled corticosteroids. This is not recognised within this document, which, as noted time and time again, is quite adult orientated. There is also no clear recognition that atopic and non-atopic children may have different response to steroids.
	5.2.5	Objective measures of lung function are usually not available for children under 5 years. Health related quality of life is not meaningful for children under 5 years and may be of limited values in slightly older children where parents' quality of life may be a more meaningful metric.

	6	How will this study deal with indirect costs such as parents' expenses? Will such expenses be picked up by the search strategy? Clearly, reducing parental costs and loss of time from work is very important in a paediatric population.
	7	There are extant studies where it seems likely that the hypothesis and study outcome are likely to be of particular interest to a particular drug company who had, in fact, sponsored both studies. Although this was mentioned in the reports, only the careful reader would have spotted it. This is an area where virtually all the work available will be drug company sponsored or drug company performed and where the most important studies (eg head to head comparisons) are often not done because of commercial self-interests. In detailing the evidence, it should be made very clear to readers who sponsored each of the studies under consideration.
	Appendix A	In terms of comparators, no mention is given to other options as add on therapy to inhaled steroids apart from long acting beta2agonists. This is a serious omission in children - both theophyline and leukotriene receptor antagonists are recommended in SIGN/BTS guidelines for this very purpose in children, and are used as such in clinical practice. This is particularly the case for the leukotriene receptor antagonists, which confer (1) protection against exercise induced asthma (a fundamental component of childhood asthma) and (2) beneficial effects in concomitant allergic rhinitis (up to 50% of kids with allergic asthma have concomitant allergic rhinitis). Not including this treatment as a comparator makes no sense.
	Appendix A	In terms of outcomes, not to include time off school is a serious omission in children.