Asthma children's report: comments that need responding to for ACD

Consultee	Comments	Response
AstraZeneca	In answering Questions 3a (ICS/LABA or similar dose ICS) and 4 (ICS/LABA in combination and in separate inhalers), AstraZeneca would have expected inclusion of the study by Pohunek et al. 2004 which investigated use of BUD/FF (Symbicort combination inhaler) vs. BUD and vs. BUD and FF (separate inhalers) and has been referred to elsewhere in the TAR. From the inclusion / exclusion criteria it is unclear why this study has been overlooked and we therefore strongly suggest its inclusion in this section.	Pohunek et al 2004 is a conference abstract and our inclusion criteria state that we would not extract, critically appraise or analyse abstracts. The study was published in full in September 2006 and was identified in our update search in October 2006 (Pohunek et al 2006). Bibliographic details of studies identified in the update search are listed in Appendix 5, and are to be included in any updates of this systematic review.
	With respect to ICS/LABA vs. ICS alone, the TAR states, "No trials were identified that assessed the effects in children of the addition of a LABA to ICS vs. a higher dose of ICS alone." However, Bisgaard (2005) has published an abstract addressing this clinical question (a paediatric substudy). The full study has been published by O'Byrne (2005), therefore the Bisgaard abstract should be included on the basis that it is within the TAR inclusion criteria: "Trials reported in abstracts or conference presentations from 2004 onwards were retrieved, however their details were not extracted, critically appraised or analysed however, details were extracted where an abstract was available which provided data supplementary to a fully published trial report of a particular study". AstraZeneca strongly suggests that the Bisgaard substudy is included for completeness.	Despite extensive searching the Bisgaard conference abstract did not appear to be indexed on any of the electronic databases we searched. We have since examined the abstract and it provides very little additional data than the O'Byrne paper. The abstract makes no cross-reference to the O'Byrne paper, or vice versa. Without prior knowledge of the O'Byrne paper the reader would be left with the impression that the total number of randomized patients was 341, when in actuality it is a potentially under-powered sub-

		group. The only results were: • Bud/form once daily (od) + as needed reduced the risk of severe exacerbation by 66% vs bud/form od ($p<0.001$) and by 51% vs bud od ($p=0.022$). • Hospitalisation/ER treatment, oral steroid and additional asthma medication use were also lower for bud/form od+as needed vs bud/form od ($p<0.001$) and bud od ($p=0.016$). • Growth was significantly greater with bud/form od+as needed (1.0 cm higher) and bud/form od (0.9 cm higher) vs bud od ($p<0.01$ for both).
	In the section assessing clinical effectiveness, there is no reference to the START (Steroid Treatment As Regular Therapy) study (Sheffer et al. 2005; Silverman et al. We recommend revising this section to incorporate these data as the START study is the largest controlled asthma study, including 1981 children.	This RCT does not meet the inclusion criteria as it is placebo controlled.
Royal College of Paediatrics and Child Health	The following study does not appear to have been considered: Verberne A, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF, Raaymakers JAM, Pocock SJ, Bogaard JM, vanNierop JC, Nagelkerke AF, Thio B, Schouten TJ, van Essen Zandvliet EEM, Denteneer A, Gerritsen J, Grol MJ, Roorda RJ, Hendriks JJE, Duiverman EJ, Kouwenberg JM, van der Laag J, Brackel HJL. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. American Journal of Respiratory and Critical Care Medicine 1998;158:213-219.	This study failed to meet the inclusion criteria as it evaluates an ICS and a LABA that are administered separately rather than in a combination inhaler.
General Practice Airways Group	We would also like to comment that there appears to be an inconsistency in statements about the relative costs of the currently available combination ICS/LABA devices between the executive summary and the main text.	The text on page 181 has been amended to be consistent with costs presented in table 27. The amended text reads

		"Symbicort is more expensive than both of the Seretide preparations that are recommended for use in children" and is consistent with results presented in the executive summary.
GSK	Three trials assessing growth were excluded, two of which compared FP with BDP and one compared FP with budesonide (BUD).	The two FP vs BDP studies appear to be conference abstracts and would not have been eligible for inclusion in the systematic review. FP vs BUD is a publication by Ferguson et al in Respiratory Medicine. This was published in 2007 and would not have been identified by our most recent search in October 2006
	Two trials included to address this question in the Report were excluded from the GSK analysis of efficacy since the doses examined are not licensed for children in the UK. Beclometasone dipropionate (BDP) is licensed up to 400µg per day in children whereas fluticasone propionate (FP) is licensed up to 800µg per day BDP equivalent.	The BTS/SIGN guidelines note that for children aged 5 to 12 years 800 mg BDP (or equivalent) is the maximum daily dose. In the study by Yiallouros and colleagues participants had been receiving between 400µg to 900µg per day of BUD/BDP (median 519 µg/m^2/day BUD, 588 µg/m^2/day). They were randomised to receive either an equal dose of BDP or an equipotent (half the dose) of FP daily. The majority of patients in

		this trial would therefore be taking doses within the BTS/SIGN guidelines.
	The Report states that there are no studies available that compared SFC with an increased dose of ICS, in an entirely paediatric population (p97). However, in the original GSK submission a trial is reported that compared SFC with both the same and an increased dose of ICS (SAM40012).	This trial is unpublished, and is only available as an abstract on the GSK-CTR. It was therefore outside the assessment inclusion criteria for which it is stated that only full trial reports or full papers will be included. Additional information on any trial in abstract form was only included if published after 2004, and supported by a full publication.
Question 3a and b.	Question 3a & b (ICS/LABA vs ICS): Although the estimation of costs is not transparent, the SFC Evohaler®[1] annual costs included in this analysis appear to be incorrect (p174) and based on the £19.50 misprint of SFC Evohaler prices in the March 2006 edition of the British National Formulary (BNF). If the correct Evohaler price of £18.14 is used, the annual cost is lower.savings associated with SFC Evohaler are increased for each of the cost comparisons undertaken in the report.	
	Assessment team response to the above statement from GSK: Due to misprint for the cost of the SFC Evohaler in the March 2006 BNF the costs listed for the comparisons of the SFC Evohaler compared with an increased dose of ICS alone are incorrect in the text and tables 19 and 21. Whilst this does not alter the overall conclusions, for clarity all the corrected cost calculations and the amended text are attached in a separate document.	
	In addition, the Symbicort®[2] 200/6 device should not be included in the cost comparisons for Question 3 (p175), as it is not licensed in children under 12 years of age.[3] The 200/12 Symbicort device is mentioned in this cost comparison but presumably this should be the 400/12 device, which is again also not licensed in this age group	The Symbicort Turbohaler device is not recommended in children under 12 years of age. The comparison with the Symbicort Turbohaler 200/6 has now therefore been deleted. The text related to question 3a has therefore now been up-dated along with the conclusions and executive

[1] Evohaler® is a trade mark of the GlaxoSmithKline group of companies
[2] Symbicort® is the trade mark of AstraZeneca AB

		summary. The amended text is now attached as a separate document. The referral to the 200/12 Symbicort device refers to the daily dose (ie) 200µg BUD/12µg FF not the specific inhaler type. This dose level has been costed from the Symbicort 100/6 Turbohaler device.
Questions 4 & 5	Due to the BNF misprint mentioned earlier the annual cost of SFC Evohaler appears to be incorrect. When the correct annual cost is included in the cost comparisons for Question 4 then the annual savings would increase to £274 and £189. For Question 5, the corrected savings are £86 and £172 per year.	Due to the mis-print in the BNF the costs in the tables and text for Seretide Evohaler are incorrect. These have been amended and are attached in the separate amended document.
	A typographical error in the Executive Summary of the Report states "the combination of BUD/FF is cheaper than those containing FP/Sal…" (page xix), which is incorrect as the evidence suggests the opposite, that the combination of FP/Sal is cheaper than BUD/FF (p183).	This has been amended.
MEDA	Response to the cost comparison analysis (section 6.11) In Figure 7 (page 162), it is claimed that the cheapest budesonide product is Pulmicort LS 50 µg at £53.50 per year. However, the cost of Novolizer 200 µg is £40.27 per year – 25% less. This is derived from: Novolizer complete 100 doses =£14.86 Novolizer refill 265 doses =£25.41 (refill cost £9.59 per 100 doses) Total = £40.27 As the device is licensed for up to 20 refills, subsequent years will cost £35.00. This is 35% less than the cost of Pulmicort LS.	Novolizer 200µg is excluded from this graph because we only undertook costings for products which are taken either 2 or 4 times per day to achieve the daily doses. This is clearly stated in the list of assumptions that were necessary in order to complete the costings.
	In Figure 8 (page 163), it is claimed that the cheapest and most expensive non-CFC-propelled budesonide product is the Pulmicort Turbohaler 100 µg at £67.50 per year. The Novolizer, at £40.27 per year (see above), costs 40% less.	Again, Novolizer 200µg is excluded from this graph because we only undertook costings for products which are taken either 2 or 4 times

	As the Novolizer device is licensed for up to 20 refills, subsequent years will cost £35.00. This is 48% less than the cost of Pulmicort Turbohaler. Novolizer should be included in the cost comparison for low-dose corticosteroids (Figures 7 and 8; pages 162–163). This will reduce the annual mean cost and budesonide (BUD) will no longer be the most expensive option.	per day to achieve the daily doses. This is clearly stated in the list of assumptions that were necessary in order to complete the costings.
	The FP costs in Figures 7 and 8 appear to be incorrect. They are based on Flixotide™ Disk Refill 50 µg being equivalent to 200 µg BDP via CFC, whereas in fact Flixotide™ Disk Refill 100 µg is equivalent to 200 µg BDP via CFC. The true cost of fluticasone propionate (FP) is therefore greater than that shown in Figures 7 and 8.	The FP costs for Figures 7 and 8 are correct. The label in the graph legend refers to the product name (ie) Flixotide Disk 50µg, not to the daily dose that is required to achieve a nominally equivalent dose with 200 µg BDP-CFC. The calculations for Flixotide disk correctly assume 2 doses of Flixotide 50µg per day = 100 µg FP per day = approx 200 µg/day BDP-CFC equivalent. Therefore at a daily cost of £0.127/per dose, the annual cost is £92.95.