Response by the

BRITISH PAEDIATRIC RESPIRATORY SOCIETY (BPRS)

to the

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE (NICE)
appraisal consultation document:

'Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years'

The BPRS acknowledges the vast amount of work and effort that has been put into collating this appraisal which deals with the commonest paediatric respiratory problem seen in both primary and secondary care in the UK.

1.1 This recommendation is in line with the SIGN National Guidelines. The BPRS trusts, however, that in some uncommon situations inhaled corticosteroids may be used outside their marketing authorisation (but perhaps only by respiratory paediatric specialists). The other consideration is that with 18 different inhaled corticosteroid preparations in almost as many devices, comparison of costs by individual clinicians is virtually impossible.

1.2 This is in line with the SIGN National Guidelines on the Management of Asthma.

2. Many members of the BPRS feel that it is important not to group together children under and above the age of 5 years. Those who wheeze above the age of 5 years are highly likely to benefit from inhaled corticosteroid (ICS) treatment. Those under 5 years of age may well not do so as the diagnosis of asthma may not be correct. Indeed, even where the diagnosis is correct the severity of the disease can vary hugely and therefore many of the statements in Section 2 are simplistic and difficult to relate to a particular clinical setting.

2.2 Which lung function test is NICE suggesting and why is it preferable to demonstrate reversibility on several occasions?

2.3 Children develop symptoms not after but *during* viral infections. The vast majority of children develop some respiratory symptoms in relation to cigarette smoke.

2.4 Many children with asthma have lung function within the normal range and therefore not all children, as they become adults, have a greater decline in lung function than the general population.

2.5 Asthma does occur in those under 5 years of age but one certainly wouldn't recommend achieving the best possible lung function in that age as we have no instruments tried and tested to do so.

Given that over 90% of children with asthma are managed in primary care, what are the recommendations about annual reviews for children over 5 years of age?

2.8 There is no ICS dose threshold for commencing add-on therapy because no suitable studies have been undertaken. The SIGN Guidelines in children are without any clear evidence base. A leukotriene receptor antagonist could be considered at any age. The evidence for this therapy even in the preschool age is poor. Members of the BPRS are concerned that NICE recommend for children younger than 2 years who do not respond to ICS, referral should be made to a respiratory paediatrician. Recurrent wheezing episodes in children in the first 2 years of life are extremely common and these frequently do not respond to ICS. Such a recommendation would lead to a vast increase in the cost of care and parental anxiety.

2.9 The evidence for *Step 4* is even less good than that for *Step 3*. The same is true for *Step 5*.

2.10 It is inappropriate to extrapolate from adult studies about compliance in paediatric patients. BPRS members would entirely agree that this is a huge issue and is likely to be of much greater relevance than the basic cost differential between the 18 different ICS preparations. There are paediatric studies which have assessed inhaler technique. Studies using adults should not be included in this appraisal document.

2.11 The use of the most appropriate inhaler device for an individual child is perhaps the most important issue in paediatric asthma management. It is not necessarily the healthcare professional's decision, it is a combined decision between that professional and the family. Guidance from NICE, SIGN or anywhere else needs to emphasise this. Doing so, however, probably negates any pharmaco-economic evaluation as it is impossible to fully incorporate this into an overall guideline

3.1 The availability of two CFC-free beclometasone preparations for use in children is likely to occur at a later stage than for adults. CFC-free issues in paediatric asthma are different to those in adult asthma.

3.2 - 4 These sections show the complexity of the licensing situation. They reflect the huge differential between adults and children demanded by the regulatory authorities and deemed necessary by the pharmaceutical industry. One can only hope that the development of the Medicines for Children Research Network will make a significant difference to this in the future.

3.5 There seems an inconsistency in the statement about combination therapy 'Only the lowest dose strength inhalers are recommended for children, and these are not recommended for individuals with severe asthma'. It is particularly in children with severe asthma that combination therapy is recommended. The statement that 'The Seretide Evohaler device is the only combined inhaler currently available that can be used with a spacer' is superfluous as the Symbicort inhaler is a dry powder inhaler and spacer devices cannot be used with such inhalers.

3.6 This information is taken directly from adult patients and is not relevant in paediatrics. There should be clear statements here about the evidence of systemic adverse effects in children.

3.7 The range of annual costs of beclometasone dipropionate, budesonide and fluticasone are remarkably similar supporting earlier comments that the most relevant cost in the management of children with asthma is using the most appropriate inhaler device and encouraging adherence to therapy.

4. BPRS members feel it is very difficult to make comments on the comparison of individual high dose, low dose or combination therapy corticosteroid treatments without being involved in the process. It is not always clear from the Appraisal why certain studies were excluded and others were not. BPRS members agree that there is a dearth of good clinical studies comparing one regime with another but it must be remembered that, in terms of efficacy, it is extremely difficult to show clinically significant differences in such studies and there continues to be wide-ranging discussion about what outcome measures are important. The fact that outcome measures in many studies show no difference does not mean to say that there is no relevant difference between regimes. It may well be that the wrong outcome measures have been used.

4.2 This economic assessment section is critically dependant on evaluation of outcome measures. Given that we have little evidence that we understand these in paediatric asthma, it is difficult to draw any conclusions from this section.

4.2.14 This section suggests that switching from beclometasone diproprionate to Seretide Evohaler increases the cost by £52, only one hospital-managed exacerbation would need to be averted for every 20 patients using the combined inhalers suggesting this may be a relatively cost-effective switch.

4.2.16 The costs of combination therapy in the same or different inhaler devices is non-interpretable without information relating to whether patients are more likely to adhere to treatment if the medication is given in one, rather than two, inhalers.

4.3.3 It appears that only 3 clinical specialists were interviewed but all three stressed the importance of distinguishing between preschool and school-aged children with asthma.

4.3.4 The evidence for NICE guidance on the use of inhaler devices in children under 5 years of age is extremely limited. An example of this is that the recommendation about the use of Turbohalers in 3-5 years of age, for instance, has no evidence base.

4.3.7 'The Committee concluded that it would be appropriate to draw on the evidence from the older age group (5-12 years) when considering treatment for the preschool age group and also to take into consideration evidence that has been available in the ICS appraisal for adults and children over the age of 12 years of age' BPRS members would universally disagree with this statement. The whole point about Medicines for Children and children of different age groups is that they are not comparable nor are they comparable with adults.

4.3.8 This brief paragraph discussed adverse events. It was very cursory but this issue is the greatest concern that parents have about the use of inhaled corticosteroids. Even if long-term growth in studies undertaken so far show no difference between the inhaled ICS, short-term growth differences may be important both clinically for professionals and emotionally for parents.

4.3.10 There is no evidence at present to support the Committee in its statement that rather than increase the dose of inhaled steroids, adding an LABA is the more appropriate option.

4.3.11 There is no specific reason why combination therapy discourages patients from stepping down treatment. In clinical practice, combination therapy can be switched to ICS treatment alone without any issue. The NICE committee discussed 'fully compliant individuals'. The suspicion is that such people do not exist.

4.3.12 The BPRS membership would agree that both combination therapies have their merits and each should be considered for each individual child.

6.1 The BPRS membership welcomes recommendations for further research. Post-marketing research on the use of combination inhalers, however, is almost exclusively confined to studies within the pharmaceutical industry. Such studies need to be encouraged through other sponsorship routes.

6.2 The BPRS is delighted about this recommendation but feels the age range needs to be limited to school-age and not below 5 years.

6.3 The BPRS is delighted at this recommendation.

Given that we have so little information about inhaler device usage, technique and compliance with therapy, the BPRS wonders if this is a recommendation for further research that NICE would consider.

Finally, it is recognised that many medications prescribed for use in children are prescribed outside their licensed recommendations. Indeed, this was the reason for the original Medicines for Children Formulary published in 1999. Inadequate studies have been undertaken over the last few decades in children and the new Medicines for Children Research Network will go some way to rectifying this. However, when considering the prescription of children's medications the BPRS would recommend that NICE looks at medications already prescribed outside their license as ignoring these would ignore a significant percentage of accepted clinical practice within paediatrics.

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