Inhaled corticosteroids and long-acting beta 2 agonists for the treatment of chronic asthma in children (under 12)

This document was commissioned by the GPIAG and authored by Dr Mike Thomas and Prof David Price, with feedback on the scope and content of the submission by members of the GPIAG

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EXECUTIVE SUMMARY

1. The majority of asthma care is provided in primary care settings, and therefore the General Practice Airways Group is delighted to contribute to the development of guidance for inhaled corticosteroids in asthma by NICE.

2. The focus of the appraisal should be on improving control of asthma with ICS. Poorly controlled asthma has an impact on individuals in terms of increased morbidity and mortality. Asthma exacerbations result in significant costs to the economy and to the NHS in terms of secondary care costs, particularly if hospitalisation is necessary. The review of ICS treatment should therefore include data on cost effectiveness of disease management, not just cost minimisation.

3. Traditional measures used in ICS studies have focused on measures of lung function and symptom scores. However this may not accurately reflect the true degree of asthma control. Other outcome measure such as exacerbation rates and health status may be more meaningful. However no single outcome measure accurately reflects asthma control and more recent studies use composite outcome measures.

4. Prescribers have to consider several factors other than the choice of molecule when initiating or increasing ICS therapy. These include
    a. ensuring that the diagnosis of asthma is correct,
    b. checking that the delivery system is correct for the patient,
    c. checking adherence with existing therapy.

5. Non-adherence is a significant issue in asthma care. Improving adherence needs to be a priority for any health professional since it puts patients at risk of exacerbations, and potentially hospitalisation, and even death. Combination products may impact adherence positively, and lead to the patient deriving greater benefit from the inhaled steroid.

6. Another factor contributing to poor control is poor inhaler technique leading to inadequate drug delivery. This is common in practice, and may influence the choice of ICS inhaler prescribed.

7. While NICE intends to focus on compounds alone in this appraisal, from practical experience it is clear that the delivery method selected may impact on the clinical outcomes achieved. In the 'real world', the compound and device are therefore closely linked. Using the same compound in different devices may achieve different outcomes. The ease with which a patient can use a particular device may well determine the compound selected for that patient.

8. It is important that recommendations for the use of ICS in asthma recognise individual heterogeneity. Because there is such variation in response, clinicians must consider a range of patient factors, and need to have a range of treatment options available in order to select the best treatment for an individual patient.

9. Many randomised controlled trials of inhaled corticosteroids in asthma have strict selection criteria for entry, which means that the RCT population may not be representative of the asthma population at large. In order that the guidance is representative and geeneralisable to the general asthma population, there is a need for this evaluation to encompass robust and methodologically sound data from 'real-world' settings including studies in milder disease, pragmatic trials and observational studies.

Key points in NICE ICS submission relating to children

10. Asthma has a high prevalence in children (12.5%-20% depending on definition)

11. Most children with asthma are treated in primary care.

12. There is evidence of undertreatment with inhaled corticosteroids (ICS) and overtreatment with high dose ICS in children.

13. Asthma diagnosis can be difficult , especially in pre-school children where objective tests are difficult to perform and confusion with other wheezing conditions can occur.

14. Clinical trials of ICS in “asthmatic” children may not therefore represent the true clinical asthma phenotype.

15. In older children randomised controlled trials of inhaled steroids tend to have narrow inclusion criteria which include lung function reversibility. This may only represent one limited asthma phenotype. Asthma is a heterogeneous condition with a variety of phenotypes. Response to inhaled corticosteroids (and ICS/LABA) combinations may vary according to phenotype e.g. the presence or not of other allergic disease.

16. In the “real world “ situation the response to inhaled corticosteroids is determined by factors other than the drug itself. One important determinant of successful asthma control is adherence to ICS therapy and another is the presence of untreated active rhinitis.

17. An important determinant of successful adherence is the choice of delivery system and inhaler technique. Other factors relate to psychosocial factors and the attitudes of the parent and child towards their medication and disease.

18. Outcome measures in trials of ICS have traditionally used measures of lung function . This has a poor correlation with symptoms and health status .Asthma exacerbations are an important outcome measure which have an economic impact on the health community, but trials need to be of sufficient power and duration to show a significant effect No single outcome measure reflects asthma control. Composite measures of asthma control may more accurately reflect the effect of the disease and the effect of any asthma therapy upon the child with asthma.

Notes:

At various points in the document we refer to ‘real world’ situations. What we mean by this is the reality of everyday practice as opposed to a clinical trial setting.

There is material in this submission relating to asthma in both children and adults. Data relating to children are woven in throughout the submission, with full supporting references. Key points relating to children are highlighted above in the Executive summary.

1. INTRODUCTION

1.1 GPIAG

The General Practice Airways Group (GPIAG) is an independent charity representing primary care health professionals interested in delivering the best standards of respiratory care. It is dedicated to achieving optimal respiratory care for all through:

- Facilitating and leading primary care respiratory research
- Promoting best practice in primary care respiratory health through education, training and other services
- Representing primary care respiratory health needs at policy level
- Supporting the development of primary care health professionals in respiratory medicine

Membership is open to any primary care health professional.

The appropriate use of inhaled corticosteroids (ICS) in asthma is of paramount importance to the management of asthma in the community. The GPIAG has played an important role in research clarifying the role of this technology in primary care settings, in educating colleagues in the use of this technology and in the production of national asthma guidelines. The GPIAG wishes to play a full and active role in these appraisals and has engaged with NICE at every stage of the appraisal process so far.

1.2 What the GPIAG and other Primary Care professional groups can contribute to the appraisal

We feel that adequate primary care input is essential for the resulting output to be relevant to the needs of primary care practitioners. We agree with the statement in the NICE guidance on the role of professional organisations in the appraisal process that ‘Healthcare professionals can provide a unique perspective of the technology within the context of current clinical practice’, and wish to represent primary care perspectives.

The guidance to professional organisations submitting to NICE appraisals makes a number of requests that we will aim to meet in this document. These include:

- The pragmatic perspective on the use of ICS and ICS with long-acting beta agonist technologies in every-day clinical practice, as opposed to controlled trials
- The way in which these technologies are currently used in the NHS, including variations in practice and opinion
- Practical implementation issues
- Generalisability issues relating to extrapolation from clinical trials to the populations encountered in clinical practice
- Additional sources of evidence that may be missed in the literature search criteria currently proposed and which may help in addressing the lack of external validity of many of the trials undertaken

We feel that there are particular factors relating to the use of these technologies in the treatment of asthma in the community that make these factors of crucial importance in this particular appraisal; these include some issues that are particularly relevant to inhaled corticosteroid therapy such as adherence, inhaler technique and issues relating to the heterogeneity of asthma and the variability of response seen at an individual level. We aim to provide evidence of how these issues may affect the appraisal and guidance resulting from it.

2. ASTHMA CARE IN THE COMMUNITY

2.1 Locus of asthma care

Most people with asthma in the UK are now managed in primary care settings alone. An Asthma UK survey in 2001 investigating asthma related health care professional contacts by people with asthma in the previous 3 years[1] showed that less than 1 in 5 patients with asthma received hospital care, while over 9/10 of patients were treated in primary care, either by a GP, an asthma nurse of by both; disturbingly, 1 in 10 patients had seen no professional at all in 3 years. The vast majority of asthma care therefore occurs in primary care settings, and it is of great importance that this is

appreciated in the formulation of recommendations for management. Other relevant factors in the community management of asthma include the central role of the asthma nurse[2;3] and the evolving role of the GP with a special clinical interest (GPwSI) in respiratory medicine[4] with over 1/3 of UK Primary Care Organisations having or planning such a service.

2.2 Scale of asthma health resource utilisation in the community

Asthma is a very common problem in the community. Over 5 million people in the UK suffer from asthma[5], and asthma results in 18,000 new asthma consultation episodes per week . The age specific prevalence rate of asthma ranges from approximately 20% in children to 10% in the over 65 years group, and has risen considerably over the last 30 years. The UK has one of the highest national prevalence rates for asthma in the world[6]. Asthma consultation rates and adverse outcomes are higher in socio-economically disadvantaged and ethnic populations[7]. Asthma results in high costs to the community both in terms of direct medical costs (pharmacy costs and healthcare utilisation costs), and in indirect costs (lost productivity costs and social care costs; in 2001 societal costs were estimated at over £2000 million[8]. However, cost of illness studies have shown that the majority of asthma costs relate to poor asthma control, accounting for up to 75% of all asthma costs [9;10]. These studies show that pharmaceutical costs amount to a minority of the total costs for asthma, and are outweighed by costs relating to poor control (principally hospitalisation costs) and by indirect costs; it is very likely therefore that more expensive technologies, including inhaled medication, that improve asthma control would result in a reduction in overall societal costs, although they may result in increased direct pharmacological costs.

We feel that the focus in this assessment should be on improving asthma control rather than limiting asthma drug costs, as improved control is likely to be a dominant economic strategy when a societal perspective is taken.

2.3 Asthma management in the community

2.3.1 Asthma diagnosis

International consensus defines asthma as: 'a chronic inflammatory disorder of the airways…symptoms are usually associated with widespread but variable airflow obstruction and an increase in airway response to a variety of stimuli'[11]. The diagnosis of asthma is now usually made in community settings, and although guidelines recommend that the diagnosis should be made on the basis of suggestive symptoms and signs and supported by documentation of changes in lung function such as peak flow variability or reversibility[12], it is recognised that the diagnosis remains a clinical one, and that a simple 'gold standard' diagnostic test does not currently exist[13]. The symptoms of asthma are non-specific and overlap with other physical and functional illnesses, and over-reliance on symptoms pattern alone may potentially lead to mis-diagnosis[14]. It is recommended that a definite diagnosis should wherever possible be made before maintenance ICS treatment is started, yet there is evidence that the diagnosis is frequently made without documentation of objective lung function abnormalities, and that ICS treatment is often instigated before a firm diagnosis has been made[15]. In addition, although the demonstration of airway calibre variability and reversible bronchoconstriction is highly specific for the diagnosis of asthma[16], the sensitivity and the positive and negative predictive values of these parameters are low[8;17;18]; the failure to demonstrate such variability does not therefore exclude asthma, particularly in milder disease. Patients who fail to demonstrate such physiological abnormalities would not satisfy the eligibility criteria for most asthma clinical trials[19], but are common in community practice and are diagnosed and treated as having asthma.

Evidence points to considerable heterogeneity in patients diagnosed as having asthma in the community. Recent UK data shows that when detailed objective investigations are performed on patients with a primary care asthma diagnosis, approximately ¼ show no objective evidence of bronchoconstriction, airways hyper-responsiveness or airways inflammation[20]. Patients referred to secondary and tertiary care clinics with previously diagnosed poorly controlled asthma have frequently been found to have other co-morbid physical or psychological problems that have accounted for their symptoms[21;22]. Diagnostic confusion with overlapping conditions such as COPD[23] and

functional breathing syndromes[24] may exist. It is likely therefore that patients diagnosed with asthma in the community have a variety of disease patterns and that many will not show the classical patterns of disease; much of the evidence base for effective interventions is therefore only generalisable with caution to the broad primary care asthma population, and there is a need for pragmatic trials with broad entry criteria and better phenotyping of asthma and asthma-like syndromes. It is also important that recognition of the need for diagnostic review is made when failure to respond to asthma therapy is found.

2.3.2 Asthma reviews.

There is evidence that structured proactive asthma care improves outcomes, and primary care asthma clinics are now commonplace[28] . GPs are encouraged to perform annual asthma reviews as part of the Quality and Outcomes Framework. At asthma reviews, primary care clinicians should assess asthma control, including current symptom levels (the Royal Collage of Physicians '3 questions'), exacerbations and lung function. Reasons for poor control should be sought including poor inhaler technique, rhinitis, limited adherence to recommended treatment regime and patient understanding and of and expectations from management. There is evidence in the UK and other countries that high levels of morbidity frequently occur in adults and in children[29;30] and that professionals frequently fail to elicit the extent of morbidity by not asking detailed and directed questions[29;31]. As a consequence under treatment or inappropriate treatment may occur resulting in avoidable morbidity. There is evidence of large variations in performance by GPs; recent UK data has indicated that the proportion of community treated adult patients receiving ICS achieving good control varies between practices from under 20% to over 80%[32].

There is now also considerable evidence that involving the patient in managing his or her asthma by the provision of education and a personal action plan results in improved satisfaction and outcomes [33;34], but unfortunately this effective strategy is under-used, and some professionals appear to doubt its effectiveness[35].

Routine asthma care is now frequently effectively delivered by trained asthma nurses, who now often make therapy decisions and may act as nurse prescribers according to agreed management protocols[2;3].

It is also important when understanding the provision of asthma care in the community to recognise that many patients are reluctant to attend for asthma reviews and continue to order repeat medication without review, and that such patients often have a poor outcome; strategies to improve review levels have included telephone review[36]. Such innovative strategies to engage with such patients appear to increase the level of patient participation in asthma review.

In summary, optimal outcomes of community asthma care occur when an accurate review of control and the reasons for poor asthma control are undertaken and a partnership is reached between the patient and the healthcare professional; this situation does not always currently occur in the UK

2.4 ICS pharmacotherapy in the community

The foundation of asthma management in the UK, including pharmacotherapy, is detailed in the BTS/SIGN UK asthma guidelines[12]. These guidelines have been produced using an explicit evidence based medicine methodology[37] and are regularly updated. ICS are the recommended treatment for persistent asthma and have an excellent efficacy and safety record at standard doses. It is now recommended however that in patients uncontrolled on standard doses of ICS, add-on therapy should be used be used before high-dose ICS are resorted to, both on efficacy and safety grounds. There is evidence however that GP prescribing does not always accord to guideline recommendations, with data indicating that high-dose and even unlicensed dose treatment is often used in community practice in the UK both in adults[38] and children[39], frequently without concomitant add-on medication. Over-treatment with ICS may occur, as there is evidence that many patients from the community are able to reduce ICS dose without loss of control, both in adults and in paediatric practice[40;41]. On the other hand, there remains evidence of under-treatment for some patients with under-use of ICS in patients with potentially avoidable morbidity[30] Although current UK guidelines make general recommendations about the order in which therapeutic options should be used to provide the best chance of success, there are still considerable areas of uncertainty for primary care practitioners, and several alterative prescribing options are available to clinicians contemplating an increase in pharmacotherapy. These options include not only decision of the ICS molecule to use

but decisions on the type of inhaler device used (eg between a pressurised metered dose inhaler (MDI), a breath-actuated pressurised metered dose inhaler (BAI) or a dry powder inhaler (DPI)), all of which are themselves available in a variety of different delivery systems. Also, in patients 'stepping up' to add-on therapy with long acting beta 2 agonists, there are decisions concerning the use of separate inhalers or fixed dose combination inhalers. A variety of factors affect clinicians decision making, including guidelines, efficacy data from RCTs, costs, assessments of patients' likely adherence to different regimes, assessments of patients' inhaler technique with different delivery systems and patient understanding and preference. Clinicians consider both the device and the individual molecule when deciding which formulation to prescribe[42].

In summary, prescribers are faced with a variety of complex decisions when deciding on which ICS formulation to use, and as a result both over-treatment and under-treatment may occur.

2.5 Factors affecting asthma control in the community.

The reasons for poor asthma control are many and complex, and a poor relationship is observed between objective measures such as lung function, bronchial hyper-reactivity and airways inflammation and asthma control[43;44]. Poor control is frequently related to factors such as adherence with ICS treatment and inhaler technique, as discussed below. Several other factors have been shown to have a significant impact on asthma outcomes independently of objective asthma severity. Outcomes of asthma care are affected by ethnicity, with black and Asian populations having poor outcomes[7;45] Socioeconomic status and depression have an effect on asthma symptoms and outcomes independent of asthma severity[46]. Stress, anxiety and depression are associated with asthma and may all lead to poor asthma control and poor asthma outcomes[5;47-49]. Functional breathing problems may complicate asthma[24]. When poor control is identified, increasing controller treatment is generally the first response, but we recommend that clinicians need to take a holistic view of the patient and his or her illness, and that decisions about initiating, increasing or changing ICS formulations are taken in conjunction with assessment of other pertinent individual factors and likely reasons for poor control in that individual. Such factors included

incorrect diagnosis or complicating co-morbidity such as COPD or dysfunctional breathing; smoking; limited adherence; poor inhaler technique and active rhinitis.

We feel therefore that recommendations on asthma pharmacotherapy need to recognise the complex needs and backgrounds of patients treated for asthma in the community.

3. ADHERENCE AND INHALER TECHNIQUE

3.1 Scale of lack of adherence in asthma

The mainstay of treatment for persistent asthma is with the regular use of ICS, and this therapy class is recommended for all but the mildest asthma[12]. Efficacy of ICS treatment will however depend on the inhaler being used regularly and as recommended (adherence), and on the drug being delivered efficiently to the airways (inhaler technique and device emission properties). It is widely accepted that adherence with recommended ICS regimes is often poor in adults and children treated for asthma. A systematic review of studies measuring adherence with ICS[50] reported that patients on average take less that 50% of inhaled medication prescribed, with different studies reporting that patients took the recommended medication on 20-73% of days, with timing of and persistence with treatment frequently being erratic.

In paediatric asthma care, numerous studies have shown that although patients and parents will report high adherence when questioned, in actuality non-adherence is common and frequent[51-56]. Poor adherence in children related to poor control[52;55;57-59], to psychological and social factors in both children and parents[53;54] and in parents to ethnicity[55] and to family dysfunction[54;55].

Poor adherence in adults is similarly common[58;60-64]; even in patients with severe persistent asthma and regular admissions only ½ use daily ICS[62]. Irregular use was commonly observed, with a 'stop-start' pattern indicative of symptom driven use described. A large UK primary care study examining the records of over 280,000 patients found that prescription refill data for ICS indicated that 58% of patients were under-using ICS medication[60], and a cross-sectional analysis of 5 GP patient populations in the UK found regular ICS use occurred in only 35% of cases[65]. As with children, factors predicting poor adherence include younger age[60] ethnicity[63], psychosocial and educational disadvantage[63;64] and health beliefs about asthma[63]. Adherence has been shown to be high immediately after a hospital admission for asthma, but to decline rapidly following discharge, with forgetfulness, misunderstanding and inconvenience being identified as causes for non-adherence[63]. Clinicians are however potentially able to improve adherence to ICS treatment in their patients; a systematic review of the effects of psycho-educational care in adults with asthma showed improvements in adherence and in outcomes in association with

educational programmes[66], and Cochrane review of patient education and provision or personal action plans in adults[33] and children[67] showed improvements in a range of asthma outcomes associated with such programmes.

3.2 Reasons for non-adherence in asthma.

Non-adherence may be intentional or non-intentional. Reasons for non-intentional compliance include forgetfulness[63;68] poor inhaler technique[50] and inconvenient regimes. There is some evidence that less inhalations per day results in better adherence, although not all studies agree on this[50].

Reasons for intentional non-adherence include personal or parental worries about the safety if ICS[69], lack of belief in the effectiveness of ICS[59;59] and over perception of asthma control[52;63;70]. Poor adherence is more likely in those with adverse psychosocial profiles[57;63;64], those with lower educational levels[63] and when poor patient-clinician communication exists[63;64;71]. The belief that asthma is an intermittent rather than a persistent illness is also associated with intermittent use of controller therapy[72]

Patients often have exaggerated concerns about the side-effects of ICS which are often mistaken and relate to misunderstandings about anabolic effects and tachyphalaxis[73]. ICS have an excellent safety profile at standard doses[74;75] but risks of caratacts[76], glaucoma[77] hip fracture[78] and even life threatening adrenal suppression in children[79] may occur with dose-related effects and log duration of use. Parents gave concerns over growth issues with children, and although the growth data from paediatric cohort studies is reasurring[80]. there are some effects on growth even at moderate licensed doses.

Actively involving patients in decision-making processes is likely to improve adherence[81].

3.3 Consequences of non-adherence in asthma

Regular use of ICS is recommended for the treatment of persistent asthma[12] as inflammation persists in periods of low or absent symptoms and the effects of ICS may take several months to be fully apparent[82]. Poor adherence is associated with

poor control in children[52;55;59] and in adults[57;62;63]. Studies have confirmed a relationship between asthma related hospitalisation and poor adherence[83], including a case control study of risk factors for asthma hospitalisation reporting that low and irregular use of ICS and a low perception of efficacy of ICS was associated with increased risk of admission[84] . A case-control study reporting typical ICS adherence rates of approximately 50% in adults compared hospitalisation rates amongst adherent and non-adherent patients; after adjusting for known potential confounders, it was reported that each 25% increase in the time without ICS medication resulted in a doubling of the asthma hospitalisation risk, and 60% of all hospitalisations would not have occurred if there had been no gaps in adherence[85]. As discussed in section 2.2 above, hospitalisation is the major driver of direct medical costs.

In a paediatric study examining the relationship between poor adherence and exacerbation frequency in childhood asthma, in those who suffered exacerbation the median compliance with ICS was 13.7% compared to 68.2% in those without exacerbations[58]. A further study found that only 18% of children hospitalised with asthma look regular ICS[86].

Large observational studies of health maintenance organisation data have shown that regular use of ICS is protective against asthma mortality[87-89] and hospitalisation[90]. Irregular use of ICS is a risk factor for diverse outcomes including death[88;89].

The consequences of poor adherence with ICS treatment can be poor outcomes, and any consideration of the effectiveness of ICS therapy needs to recognise that adherence is a key issue

In summary, non-adherence is a significant issue in asthma care. Improving adherence needs to be a priority for any health professional since it puts patients at risk of exacerbations, and potentially hospitalisation, and even death.

3.4. Inhaler Technique

The efficacy of inhaled therapy relies on delivery of inhaled medication to the airways and therefore on adequate inhaler technique. Poor inhaler technique may therefore result in lack of adequate lung deposition and so in treatment failure[91]. Although patients entered into randomised controlled trials of inhaled therapy are selected on the basis of an adequate inhaler technique, there is considerable evidence that inhaler

technique is often inadequate in clinical practice. A review of 6 studies comparing major problems with inhalation technique in patients treated for asthma using various self-actuated inhaler devices found significant problems in technique in between 58 and 89% of patients[92]. A further systematic review of studies quantifying the fraction of patients using the inhaler correctly on the basis of a physician assessment found 'good' technique in between 5 and 86% of patient depending on how intensively trained patients had been and what device they were using[50] and overall found 'efficient' technique in about 50% or patients. Training appears effective in improving technique[50;93] but does not always occur in real world situations. This problem seems to be most acute in association with MDIs[94;95], where problems with technique include poor co-ordination between the actuation of the aerosol and commencement of the correct inhalational effort and a slow inhalation[96;97] and may lead to inadequate drug deposition in the lungs.

In paediatric practice, a recent review paper quoted correct technique in 39-67% of children with asthma[98], and in a recent study only 2 or 30 children assessed had adequate technique, although in all cases the parents thought that the technique was good [99].

In summary, poor inhaler technique leading to inadequate drug delivery is common in real-world practice, and may influence the choice of ICS inhaler prescribed.

3.5 Choice of formulation and outcomes

ICS are available in a variety of formulations in the UK, including MDIs, BAIs and DPIs. Even with good technique the amount of active drug reaching the lungs varies with the type of delivery system used, and depend on a number of factors including the pharmacokinetic and dynamic properties of the formulation. Deposition studies indicate improved delivery of drug with a DPI over MDIs[100] and with a BAI over an MDI[100;101]

An important question for clinicians is therefore whether the choice of formulation and delivery system has an effect on asthma clinical outcomes. A systematic review of randomised controlled trials comparing the clinical effectiveness of the delivery of ICS via different delivery systems[102] concluded that there was no evidence of improved efficacy with the more expensive and sophisticated BAI or DPI devices. The generalisability of the results of this study have however been criticised;

examination of the inclusion criteria of the studies included in this meta-analysis shows that good inhaler technique with either device and good compliance were prerequisites to entry in the study. Indeed, as discussed below, there is considerable evidence that the inclusion criteria for many asthma RCTs means that only 5% of people treated for asthma in the community would be eligible for such studies, and hence casts significant doubt on the uncritical extrapolation of the results of these studies to the many patients with asthma with poor compliance and poor inhaler technique[19;103]. Senior UK asthma experts have questioned whether improved compliance and improved drug deposition that may be associated with DPIs or BAIs above MDIs may result in better outcomes and so may be more cost effective[104]. Evidence from UK observational studies encompassing the heterogeneous 'real-life' asthma population suggests that outcomes may be better in those prescribed BAIs above those prescribed MDIs[105], and in those prescribed a DPI above those prescribed an MDI[106]. There is also evidence of differences in outcome in patients prescribed the same ICS molecule via different DPI systems[107].

In addition, for some patients the use of a combination inhaler incorporating an ICS and a bronchodilator (e.g. ICS plus long acting beta agonist) may result in greater adherence and so in improved outcomes; a study assessing refill rates in a US health maintenance organisation report that adherence and persistence with ICS treatment was higher in those prescribed a combination formulation than in those prescribed an ICS alone (4.1 v 2.3 refills/12months), or than those prescribed the 2 components in separate inhalers[108]; it is suggested that patients are able to perceive the immediate benefits of the bronchodilator component of a combination inhaler more immediately than the delayed effects if the ICS, and the confidence provided by this perception may improve adherence with the ICS.

While NICE intends to focus on compounds alone in this appraisal, from a primary care perspective it is clear that the delivery method selected may impact on the clinical outcomes achieved, with significant sequelae for morbidity and mortality . In the 'real world', the compound and device are therefore closely linked. Using the same compound in different devices may achieve different outcomes.

4. CO-MORBIDITY

A number of co-morbid conditions exist that can affect asthma control and the results of asthma pharmacotherapy and these need to be considered by clinicians when considering therapeutic options in asthma.

4.1 Allergic Rhinitis

Asthma and rhinitis are commonly associated with each other[109], and the WHO has recommended that when one diagnosis is made the presence of the other condition should be actively looked for[110], and that when co-morbidity exists a strategy that encompasses treatment of both upper and lower airways inflammation may provide the best outcomes. UK primary care studies have shown that the presence of co-morbid rhinitis may be a marked for poor asthma outcomes both in adults[111;112] and in children[113]. When co-morbidity exists, asthma outcomes may be better in those in whom the rhinitis is treated[114;115]. However, when topical therapy with corticosteroids is given for each condition, the cumulative steroid load needs to be considered particularly when the nasal corticosteroid used is orally bioavailable[77;116].

4.2 Gastro-oesophageal Reflux

Gastro-oesophageal reflux is more common in people with asthma[117] and reflux can give rise to respiratory symptoms and to worsened asthma[118]; the relationship between asthma and reflux appears to be bi-directional[119]. Some patients with co-morbidity may show better asthma outcomes when reflux is treated[120].

4.3 Smoking

Many patients with asthma smoke, and until recently little evidence was available on such patients as they were generally excluded from clinical trials. It has become clear however that asthma outcomes are poor in smokers[121] and that smoking leads to

steroid-resistant disease requiring significantly higher doses of ICS for effective treatment[97].

5. HETEROGENEITY OF ASTHMA AND ASTHMA OUTCOMES

5.1: Asthma Phenotypes

Asthma is a heterogeneous condition[122] and different patients may respond in different ways to different therapies[123;124]. There is a heterogeneity in individual patient dose-response relationships to ICS[125;126]; while many patients will achieve maximum ICS responses at doses between 400 and 800 mcg/day of beclomethasone or equivalent[127], some patients with more therapy-resistant disease uncontrolled on standard doses of ICS may benefit from higher doses[128;129]. " A significant minority of patients may show resistance to ICS therapy. A large multinational study of 3416 uncontrolled asthma patients (Bateman, Boushey et al, Am J Res Crit Care Med, 2004;170:835-44) showed that in spite of attempts to optimise asthma control with individualised doses of an inhaled steroid/ long acting beta agonist combination about 30 % of patients failed to achieve Guideline-recommended control." Guidelines and guidance make recommendations based on grouped mean data from clinical trials, and these data point to the therapeutic option that is most likely to be successful. It is important to recognise however that the grouped mean data will encompass considerable individual variation in response, and there may be sub-groups responding particularly well or badly to particular therapies. It is therefore important to recognise that not all patients will require or respond well to the same therapy. It is starting to become apparent that in part this heterogeneity relates to genetic factors[130]. Phenotypes of asthma are beginning to be described[131], some of which have implications for therapeutic effect; for example, asthma characterised by neutrophilic rather than eosinophilic airways inflammation is highly steroid-resistant[132]. The influence of co-morbidities, ethnicity, psychosocial factors and factors such as smoking on asthma outcomes is discussed above.

It is important therefore that recommendations for the use of ICS in asthma recognise individual heterogeneity, that a significant minority of asthma patients are not controlled with inhaled ICS treatment, and that guidance does not prevent clinicians from having a range of compounds to choose from.

5.2: Outcome measures in asthma

Asthma is a complex and multi-faceted condition and no single outcome measure encompasses the whole picture in asthma[133]. Relevant outcome measures in the assessment of asthma control include lung function, symptoms, health status, exacerbations, lung function, measures of airways inflammation and of airways hyper-reactivity. No single outcome measure can give sufficient information in isolation on asthma control, and composite measures are increasingly used as outcome measures in asthma clinical trials[134]. There is for instance a poor relationship between symptoms and lung function[44]. Treatment strategies targeted on inflammation[132;135] or hyper-reactivity[136] may lead to better outcomes than traditional guideline based assessments centring on symptom control and lung function.

5.3: Duration of asthma studies

It has been increasingly recognised that duration of asthma studies are important when examining outcomes. Whilst 12 weeks may be sufficient to study lung function response, it is clearly inadequate to assess exacerbations and broad asthma control. Longer term studies are also required when examining the impact of adherence on asthma outcomes related to different technologies.

6. DATA SOURCES

Modern guidelines and treatment decision protocols rely on evidence-based recommendations, and evidence from randomised controlled trials (RCTs) and systematic reviews of such trials are given highest credence and the highest evidence levels in guidelines. The NICE evaluation plans to follow this paradigm. It needs to be borne in mind however that the structure of the RCT is designed to show internal validity by removing possible sources of bias; this includes strict entry criteria that encompass precise demographic and phenotypic characterisation of subjects. When extrapolating the results of RCTs to broader populations beyond the study recruitment base, it is however critically important to show external validity, i.e. to confirm that the study population is broadly similar to the general population for whom the guidance is intended.

A recent study of eligibility criteria investigated whether patients attending GP and outpatient clinics for asthma treatment would fulfil the typical entry criteria for asthma clinical trials (absence of co-morbidity, FEV1 50–85% of predicted, present or historical reversibility of 12% in the last year, non-smoker or if ex-smoker with a smoking burden of less then 10 pack years) found that only 5% of 334 consecutive patients met these criteria[19]; if additional criteria such as being symptomatic and having regular use of inhaled corticosteroids were added this reduced the numbers of eligible asthma patients to 3.3%. This paper questioned whether such data can be extrapolated to a larger, ‘‘real life’’ population of patients with asthma. Indeed, it has been suggested that manipulation of study entry criteria and outcome measures by study sponsors in asthma clinical trials may lead to superiority of particular products or therapy classes[103]; for instance, a study designed to examine the efficacy of a bronchodilator is more likely to be positive if patients with reduced lung function and documented reversibility to bronchodilators are used as entry selection criteria, and a study wishing to show superiority of an anti-inflammatory medication is more likely to be positive if patients with demonstrated sub-optimally treated inflammation are selected, and if exacerbations are the principle outcome measure. These issues clearly need to be carefully appraised when reviewing study evidence sources.

There is evidence to suggest that GPs may harbour reservations about the applicability of EBM conclusions to their practice and to the patients that they treat. Recent qualitative studies of UK GPs [137;138] suggest that their views of effective care

encompassed not only the objective clinical factors addressed in RCTs but also covered individual patient factors and the resource related factors that play a role in 'real-world' practice. They also felt that evidence resulting from hospital-based patients and settings did not necessarily apply to the 'real-world' setting they practised in, and received a tension between 'evidence-based specialist and 'pragmatic' generalists[138]. A recent meta-analysis of effective interventions for changing clinical behavior found that successful interventions needed to be perceived as relevant by GPs to the patients that they see and to the in which context that they practice[139].

We feel therefore that there is a need for this evaluation to encompass robust and methodologically sound data from 'real-world' settings including studies in milder disease, pragmatic trials and observational studies.

7. SUMMARY

The GPIAG supports a review of the use of ICS technologies in the treatment of asthma. We feel however that this review must encompass real world considerations, which will involve using data sources beyond RCT data and careful consideration of the external validity of randomised trial data. There are particular factors in the assessment of this technology that necessitate this ‘real-world’ perspective; in particular issues of adherence and inhaler technique are of crucial importance in assessing the use of ICS treatment for asthma. The considerable heterogeneity of asthma and the complexity of managing asthma means that a simple recommendation of one compound over others may not benefit patient outcomes.

Reference List

1. National Asthma Campaign. Out in the open, a true picture of asthma in the United Kingdom today: the NAC asthma audit 2001. *Asthma J* 2001;**6**:1-14.

2. Kamps AWA, Roorda RJ, Kimpen JLL, et al. Impact of nurse-led outpatient management of children with asthma on healthcare resource utilisation and costs. *European Respiratory Journal* 2004;**23**:304-9.

3. Morice AH,.Wrench C. The role of the asthma nurse in treatment compliance and self-management following hospital admission. *Respir Med* 2001;**95**:851-6.

4. Pinnock H, Netuveli G, Price D, Sheikh A. General practitioners with a special interest in respiratory medicine: national survey of UK primary care organisations. *BMC Health Serv Res* 2005;**5**:40.

5. Smith NM. The 'Needs of People with Asthma' survey and initial presentation of the data. *Asthma J* 2000;**5**:133-6.

6. British Thoracic Society. The Burden of Lung Disease. British Thoracic Society . 2002.

7. Netuveli G, Hurwitz B, Levy ML, Fletcher M, Barnes G, Durham SR *et al*. Ethnic variations in UK asthma frequency, morbidity, and health-service use: a systematic review and meta-analysis**.** *Lancet* 2005;**365**:321-17.

8. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P *et al*. Diagnosing Asthma- Comparisons between Exhaled Nitric Oxide Measurements and Conventional Tests. *Am J Respir Crit Care Med* 2004;**169**:473-8.

9. Barnes PJ, Jonsson B, Klim JB. The costs of asthma. *Eur Respir J* 1996;**9**:636-42.

10. Stevens CA, Turner D, Kuehni CE, Couriel JM, Silverman M. The economic impact of preschool asthma and wheeze. *Eur Respir J* 2003;**21**:100-1006.

11. International consensus report on the diagnosis and treatment of asthma. *Eur Respir J* 1992;**5**:601-41.

12. British Thoracic Society,.Scottish Intercollegiate Guideline Network. British Guidelines on the Management of Asthma. *Thorax* 2003;**58**:1-94.

13. Britton J,.Lewis S. Objective measures and the diagnosis of asthma. *BMJ* 1998;**317**:227-8.

14. Joyce DP, Chapman KR, Kesten S. Prior diagnosis and treatment of patients with normal results of methacholine challange and unexplained respiratory symptoms. *Chest* 1996;**109**:697-701.

15. Dennis S, Price JF, Vickers M, Frost CD, Levy ML, Barnes PJ. The management of newly identified asthma in primary care in England. *Prim Care Resp J* 2002;**11**:120-2.

16. Lewis SA, Weiss ST, Britton JR. Airway reponsiveness and peak flow variability in the diagnosis of asthma for epidemiological studies. *Eu Respir J* 2001;**18**:921-7.

17. Hunter CJ, Brightling C, Woltmann G, et al. *Chest* 2002;**121**:1051-7.

18. Goldstein MF, Veza BA, Dunsky EH, et al. Comparisons of Peak Diurnal Expiratory Flow Variation, Postbronchodilator FEV1 Responses, and Methacholine Inhalation Challenges in the Evaluation of Suspected Asthma. *Chest* 2001;**119**:1010.

19. Herland K, Akselsen JP, Skjonsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger & 'real life' population of patients with obstructive lung disease? *Respiratory Medicine* 2005;**99**:11-9.

20. Shaw DE, Mellor S, Berry MA, Hargadon B, McKenna S, Shelley M *et al*. D E Shaw, S Mellor, M A Berry, B Hargadon, S McKenna, M Shelley, H

Pateman, R H Green, A J Wardlaw, B McKinley, M Thomas and I D Pavord. Patterns of airflow limitation in patients with a primary care diagnosis of asthma, and their relationships to eosinophilic inflammation (Abstract). *Thorax* 2005;**60**.

21. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct? *Fam Pract* 1999;**16**:112-6.

22. Heaney L,.Robinson D. Severe asthma treatment: need for characterising patients. *Lancet* 2005;**365**:974-6.

23. Tinkelman DG, Price D, Nordyke RJ, Halbert RJ. Misdiagnosis of COPD and Asthma in Primary Care Patients 40 Years of Age and Over. *J Asthma* 2006;**43**:75-80.

24. Thomas M, McKinley RK, Freeman E, Foy C. Prevalence of dysfunctional breathing in patients treated for asthma in primary care: cross sectional survey. *BMJ* 2001;**322**:1098-100.

25. Martinez F. Development of wheezing disorders and asthma in preschool children. *Pediatrics* 2002;**109**:129-32.

26. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. *N Eng J Med* 1995;**332**:888-994.

27. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood (Cochrane Review) In The Cochrane Library of systematic reviews. Chichester, UK: John Wiley & Sons, Ltd, 2006.

28. Ram FSF, Jones A, Fay JK. Primary care based clinics for asthma (Cochrane Review). In: The Cochrane Library, Issue 1. Chichester, UK: John Wiley & Sons, Ltd., 2006.

29. Price D, Ryan D, Pearce L, Bawden R, Freeman D, Thomas M *et al*. The burden of paediatric asthma is higher than health professionals think: results from the Asthma In Real Life (AIR) study. *Prim Care Respir.J* 2002;**11**:30-3.

30. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;**16**:802-7.

31. Price D, Ryan D, Pearce L, Bride F. The AIR study: asthma in real life. *Asthma J* 1999;**4**:74-8.

32. Price D, Horne R, Ryan D, Freeman D., Lee A. Large variations in asthma control between UK general practices participating in the asthma control, concordance and tolerance (ACCT) Initiative. *Prim Care Resp J* 2006;**in press (abstract)**.

33. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, Bauman A, Hensley MJ, and Walters EH. Self-management education and regular practitioner review for adults with asthma. The Cochrane Library Issue 1. 2003. Oxford: Update Software.

34. Turner MO, Taylor D, Bennett R, Fitzgerald JM. A randomized trial comparing peak expiratory flow and symptom self-management plans for patients with asthma attending a primary care clinic. *Am J Respir Crit Care Med* 1998;**157**:540-6.

35. Jones A, Pill R, Adams S. Qualitative study of views of health professionals and patients on guided self management plans for asthma. *BMJ* 2000;**321**:1507-10.

36. Pinnock H, Bawden R, Proctor S, Wolfe S, Scullion J, Price D *et al*. Accessibility, acceptability, and effectiveness in primary care of routine telephone review of asthma: pragmatic, randomised controlled trial. *BMJ* 2003;**326**:477.

37. Scottish Intercollegiate Guidelines Network. SIGN 50: a guideline developers' handbook. Edinburgh: SIGN, 2002.

38. Thomas M, Turner S, Leather D, Price D. High dose inhaled corticosteroid use in childhood asthma: an observational study. *BJGP* 2006;**in press**.

39. Thomas M, Leather D, Price D. High dose inhaled corticosteroids and add-on therapy use in adults in te UK in 2003: an observational study. *Prim Care Respir.J* 2006;**15**:166-72.

40. Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. *BMJ* 2003;**326**:1115.

41. Visser MJ, van der Veer E, Postma DS, Arends LR, de Vries TW, Brand PL *et al*. Side-effects of fluticasone in asthmatic children: no effects after dose reduction. *Eur Respir J* 2004;**24**:420-5.

42. Price D. Do healthcare professionals think that dry powder inhalers can be used interchangeably. *Int J Clin Pract* 2005;**149**:26-9.

43. Leuppi JD, Salome CM, Jenkins CR, et al. Predictive markers of asthma exacerbation during stepwise dose reduction of inhaled corticosteroids. *Am J Respir Crit Care Med* 2001;**163**:406-12.

44. Teeter JG,.Bleecker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. *Chest* 1998;**113**:277.

45. Griffiths C, Kaur G, Gantley M, et al. Influences on hospital admission for asthma in south Asian and white adults: qualitative interview study. *BMJ* 2001;**323**:962-6.

46. Rimington LD, Davies DH, Lowe D, Pearson MG. Relationship between anxiety, depression, and morbidity in adult asthma patients. *Thorax* 2001;**56**:266-71.

47. Sandberg S, Paton J, Ahola S, McCann DC, McGuinness D, Hillary CR *et al*. The role of acute and chronic stress in asthma attacks in children. *Lancet* 200;**356**:982-7.

48. Sandberg S, Jarvenpaa S, Penttinen A, Paton J, McCann DC. Asthma exacerbations in children immediately following stressful life events: a Cox's hierarchical regression. *Thorax* 2004;**59**:1046-51.

49. Hasler G, Gergen PJ, Kleinbaum DG, Ajdacic V, Gamma A, Eich D *et al*. Asthma and panic in young adults. *Am J Respir Crit Care Med* 2005;in press.

50. Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Jospeh RH. Inhaled Corticosteroids for Asthma Therapy: patient Compliance, Devices and Inhalation Technique. *Chest* 2000;**117**:542-50.

51. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Childrens Compliance with Inhaled Asthma Medications. *Journal of Allergy and Clinical Immunology* 1995;**95**:217.

52. Kuehni CE,.Frey U. Age-related differences in perceived asthma control in childhood: guidelines and reality. *European Respiratory Journal* 2002;**20**:880-9.

53. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. *Journal of Allergy and Clinical Immunology* 1996;**98**:1051-7.

54. Bender B, Milgrom H, Rand C, Ackerson L. Psychological factors associated with medication nonadherence in asthmatic children. *Journal of Asthma* 1998;**35**:347-53.

55. Bender B, Wamboldt FS, O'Connor SL, Rand C, Szefler S, Milgrom H *et al*. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. *Annals of Allergy Asthma & Immunology* 2000;**85**:416-21.

56. Bender B, Bartlett S, Rand C, Turner C, Wamboldt F, Zhang L. Objective measurement of adherence with asthma medications. *Journal of Allergy and Clinical Immunology* 2006;**117**:S265.

57. Schatz M, Mosen D, Apter AJ, Zeiger RS, Vollmer WM, Stibolt TB *et al*. Relationship of validated psychometric tools to subsequent medical utilization for asthma. *Journal of Allergy and Clinical Immunology* 2005;**115**:564-70.

58. Milgrom H,.Bender B. Nonadherence with the asthma regimen. *Pediatric Asthma Allergy & Immunology* 1997;**11**:3-8.

59. Irvine L, Crombie IK, Alder EM, Neville RG, Clark RA. What predicts poor collection of medication among children with asthma? A case-control study. *European Respiratory Journal* 2002;**20**:1464-9.

60. van Staa TP, Cooper C, Leufkens HGM, Lammers JW, Suissa S. *Respir Med* 2003;**97**:578-85.

61. Dompeling E, Van Grunsven PM, Van Schayck CP, Folgering H, Molema J, Van Weel. Treatment with inhaled steroids in asthma and chronic bronchitis: long-term compliance and inhaler technique. *Fam Pract* 1992;**9**:161-6.

62. Legorreta AP, Christian-Herman J, O'Connor R, Hasan MM, Evans R, Evans R. Compliance with national asthma management guidelines and specialty care: a health maintenance organization experience. *Arch Intern Med* 1998;**158**:457-64.

63. Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. Adherence with twice-daily dosing of inhaled steroids - Socioeconomic and health-belief differences. *Am.J.Respir.Crit.Care Med.* 1998;**157**:1810-7.

64. Apter AJ, Boston RC, George M, Norfleet AL, Tenhave T, Coyne JC *et al*. Modifiable barriers to adherence to inhaled steroids among adults with asthma: It's not just black and white. *Journal of Allergy and Clinical Immunology* 2003;**111**:1219-26.

65. Walsh LJ, Wong CA, Cooper S, Guhan AR, Pringle M, TattersfieldAE. Morbidity from asthma in relation to regular treatment: a community-based study. *Thorax* 1999;**54**:296-300.

66. Devine E. Meta-analysis of the effects of psychoeducational care in adults with asthma. *Res Nurs Health* 1996;**19**:367-76.

67. Wolf FM, Guevara JP, Grum CM, Clark NM, Cates CJ. Educational interventions for asthma in children. *The Cochrane Database of Systematic Reviews* 2006.

68. Buston KM,.Wood SF. Non-compliance amongst adolescents with asthma: listening to what they tell us about self-management. *Fam Pract* 2000;**17**:134-8.

69. Chan PW,.DeBruyne JA. Parental concern towards the use of inhaled therapy in children with chronic asthma. *Pediatr Int* 2000;**42**:547-51.

70. Kim C, Feldman HI, Joffe M, Tenhave T, Boston R, Apter AJ. Influences of earlier adherence and symptoms on current symptoms: A marginal structural models analysis. *Journal of Allergy and Clinical Immunology* 2005;**115**:810-4.

71. George M, Freedman TG, Norfleet AL, Feldman HI, Apter AJ. Qualitative research-enhanced understanding of patients' beliefs: Results of focus groups with low-income, urban, African American adults with asthma. *Journal of Allergy and Clinical Immunology* 2003;**111**:967-73.

72. Halm EA, Mora P, Leventhal H. No symptoms, no asthma - The acute episodic disease belief is associated with poor self-management among inner-city adults with persistent asthma. *Chest* 2006;**129**:573-80.

73. Boulet LP. Perception of the role and potential side effects of inhaled corticosteroids among asthmatic patient. *Chest* 1998;**113**:578-92.

74. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids: new developments. *Am J Respir Crit Care Med* 1998;**157**:S1-S53.

75. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999;**159**:941-4.

76. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Eng J Med* 1997;**337**:8-14.

77. Garbe E, LeLorier J, Boivin JF. Inhaled and nasal glucocorticoids and the risk of occular hypertension or open-angled glaucoma. *JAMA* 1997;**277**:722-7.

78. Hubbard RB, Smith CJP, Smeeth L, Harrison TW, Tattersfield AE. Inhaled Corticosteroids and Hip Fracture.A Population-based Case–Control Study. *Am J Respir Crit Care Med* 2002;**166**:1563-6.

79. Todd GRD, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002;**87**:457-61.

80. Allen DB. Inhaled corticosteroid therapy for asthma in preschool children: growth issues. *Pediatrics* 2002;**109**:373-80.

81. Chambers CV, Markson L, Diamond JJ, et al. Health beliefs and compliance with inhaled corticosteroids by asthmatic patients in primary care practices. *Respir Med* 1999;**93**:88-94.

82. Dollery C (ed.). Therapeutic Drugs. Edinburgh: Churchill Livingstone, 1999.

83. Halm EA, Wisnivesky JP, Leventhal H. Quality and access to care among a cohort of inner-city adults with asthma: who gets guideline concordant care? *Chest* 2005;**128**:1943-50.

84. van Ganse E, Hubloue I, Vincken W, Leufkens HGM. Actual use of inhaled corticosteroids and risk of hospitalisation: a case-control study. *Eur J Clin Pharmacol* 1997;**51**:449-454Eur J Clin Pharmacol.

85. Williams LK, Pladevall M, Xi H, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *Journal of Allergy and Clinical Immunology, The* 2004;**114**:1288-93.

86. Scarfone RJ, Zorc JJ, Capraro GA. Patient self-management of acute asthma: Adherence to national guidelines a decade later. *Pediatrics* 2001;**108**:1332-8.

87. Ernst P, Spitzer WO, Suissa S, Cockcroft D, Habbick B, HorwitzRI *et al*. Risk of fatal and near-fatal asthma in relation to inhaled corticosteroid use. *JAMA* 1992;**268**:3462-4.

88. Suissa S, Elphick HE, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Eng J Med* 2000;**343**:332-6.

89. Suissa S,.Ernst P. Inhaled corticosteroids: Impact on asthma morbidity and mortality. *Journal of Allergy and Clinical Immunology, The* 2001;**107**:937-44.

90. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002;**57**:880-4.

91. Lindgren D, Blake B, Larrson S. Clinical consequences of inadequate inhalation technique in asthma. *Eur J Respir Dis* 1987;**70**:93-8.

92. Duerden M,.Price D. Training issues in the use of inhalers. *DisManage Health Outcomes* 2001;**9**:75-87.

93. Basheti IA, Reddel H, Armour CL, et al. Counseling about Turbuhaler technique: Needs Assessment and Effective Strategies for Community Pharmacists. *Respir Care* 2005;**50**:617-23.

94. Lenney W, Innes A, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference for seven inhaler devices. *Respir.Med.* 2000;**98**:496-500.

95. Larsen JS, Hahn M, Ekholm B, Wick KA. Evaluation of conventional press-and-breathe metered-dose inhaler technique in 501 patients. *J Asthma* 1994;-192.

96. Pauwels R, Newman S, Borgstrom L. Airway deposition and airway effects of antiasthma drugs delivered from metered-dose inhalers. *Eur J Respir Dis* 1997;**10**:2127-38.

97. Tomlinson HS, Corlett SA, Allen MB, Chrystyn H. Assessment of different methods of inhalation from salbutamol metered dose inhalers by urinary drug excretion and methacholine challenge. *Brit J Clin Pharmacol* 2005;**60**:605-10.

98. Devadason SG. Recent advances in aerosol therapy for children with asthma. *Int J Clin Pract* 2005;**149**:19-25.

99. Winkelstein ML, Huss K, Butz A, Eggleston P, Vargas P, Rand C. Factors associated with medication self-administration in children with asthma. *Clin Pediatr* 2000;**39**:337-45.

100. Borgstrom L, Derom E, Stahl E, et al. The inhalational device influences lung deposition and bronchodilating effects of terbutaline. *Am J Respir Crit Care Med* 1996;**153**:1636-40.

101. Newman SP, Talaee N, et al. Improvement of delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. *Thorax* 1991;**46**:712-6.

102. Brocklebank D, Wright J, Cates C. Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering corticosteroids in asthma. *BMJ* 2001;**323**:896.

103. Bjermer L. Evidence-based recommendations or "Show me the patients selected and I will tell you the results". *Respiratory Medicine***In Press**.

104. Barnes PJ. Asthma guidelines: recommendations versus reality. *Respir.Med* 2004;**98**:S1-S7.

105. Price D, Thomas DM, Mitchell G, Niziol C, Featherstone R. Improvement of asthma control with a breath actuated pressurisedmetred dose inhaler (BAI): a prescribing claims study of 5556 patients using a traditional pressurisedmetred dose inhaler (MDI) or a breath-actuated device. *Resp Med* 2003;**97**:12-9.

106. Price D,.Thomas M. Improved asthma outcomes associated with inhaled corticosteroids delivery via a dry powder rather than metered dose inhaler. *Thorax* 2004;**39**:72.

107. Thomas M,.Williams AE. Are outcomes the same with all dry powder inhalers? *Int J Clin Pract* 2005;**59**:33-5.

108. Stoloff SW, Stempel DA, Meyer JW, Stanford RH, Carranza Rosenwig JR. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *Journal of Allergy and Clinical Immunology, The* 2004;**113**:245-51.

109. Gaugaris S, Sazonov-Kocevar V, Thomas M. Burden of concomitant allergic rhinitis in adults with asthma. *J Asthma* 2006;**43**:1-7.

110. Bousquet J V-CPKNatAg. Allergic rhinitis and its impact on asthma. *J Allergy Clim Immunol* 2001;**108 (suppl)**:S147-S333.

111. Yawn BP, Yunginger JW, Wollan PC, et al. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. *J Allergy Clim Immunol* 2006;**103**:54-9.

112. Price D, Kocevar VS, Zhang Q, Yin D, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy* 2005;**35**:282-7.

113. Thomas M, Kocevar VS, Zhang Q, Yin D, Price D. Asthma-related health care resource use amongst asthmatic children with and without concomitant allergic rhinitis. *Pediatrics* 2005;**115**:129-34.

114. Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: The risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 2002;**108**:57-62.

115. Corren J, Manning BE, Thompson SF, et al. Rhinitis therapy and the prevention of hospital care for asthma: A case-control study. *J Allergy Clin Immunol* 2004;**113**:415-9.

116. Ekins-Daukes S, Simpson CR, Helms PJ, et al. Burden of corticosteroids in children with asthma in primary care: retrospective observational study. *BMJ* 2002;**324**:1374.

117. Harding SM,.Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. *Chest* 1997;**111**:1389-402.

118. Gastal OL, Castell JA, Castell D. Frequency and site of gastroesophageal reflux in patients with chest symptoms: studies using proximal and distal pH monitoring. *Chest* 1994;**106**:1739-96.

119. Ruigomez A, Rodriguez LAG, Wallander M, Johansson S, Thomas M, Price D. Gastroesophageal Reflux Disease and Asthma: A Longitudinal Study in UK General Practice. *Clin Exp Allergy* 2005;**128**:85-93.

120. Gibson PG, Henry RL, Coughlan J. Gastro-oesophageal reflux treatment for asthma in adults and children *The Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd, 2006.

121. Laforest L, van Ganse E, Devouassoux G, et al. Influence of patients' characteristics and disease management on asthma control. *Journal of Allergy and Clinical Immunology, The* 2006;**117**:1404-10.

122. Weiss ST. Epidemiology and heterogeneity of asthma. *Annals of Allergy, Asthma, and Immunology* 2001;**77**:5-8.

123. Malmstrom K, Rodriguez-Gomer G, Guerra L, et al. Oral montelukast, inhaled beclomethasone and placebo for chronic asthma: A randomised controlled trial. *Ann Intern Med* 1999;**130**:487-95.

124. Zeiger RS, Szefler S, Phillips B, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. *Journal of Allergy and Clinical Immunology, The* 2006;**117**:45-52.

125. Szefler S, Martin RJ, King TS, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. *Journal of Allergy and Clinical Immunology, The* 2002;**109**:410-8.

126. Adams NP, Bestall JP, and Jones PW. Inhaled beclomethasone versus placebo for chronic asthma (Cochrane review). The Cochrane Library (Issue 3). 2001. Oxford: Update Software.

127. Masoli M, Holt S, Wetherall M, Beasley R. Dose-response relationship of inhaled budesonide in adult asthma: a meta-analysis. *Eur Respir J* 2004;**23**:552-8.

128. Pauwels R, Löfdahl CG, Postma D, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;**337**:1405-11.

129. Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG *et al*. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;**58**:211-6.

130. Israel E, Drazen JM, Liggett SB, Boushey HA, Cherniack RM, Chinchilli VM *et al*. The effect of polymorphisms of the b2 adrerngicreceptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med* 2000;**162**:75-80.

131. Wardlaw AJ, Silverman M, Siva R, Pavord ID, Green RH. Multi-dimensional phenotyping: towards a new taxonomy for airway disease. *Clin Exp Allergy* 2005;**35**:1054-62.

132. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw A, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002;**57**:875-9.

133. Barnes N. Outcome measures in asthma. *Thorax* 2000;**55 (suppl 1)**:S70-S74.

134. Bateman ED, Boushey HA, Bousquet J, et al. Can Guideline-defined Asthma Control Be Achieved? The Gaining Optimal Asthma ControL Study. *Am J Respir Crit Care Med* 2004;**170**:836-44.

135. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of Exhaled Nitric Oxide Measurements to Guide Treatment in Chronic Asthma. *N Engl J Med* 2005;**352**:2163-73.

136. Sont JK, Willelms LNA, Bell EH, et al. Clinical Control and Histopathologic Outcome of Asthma when Using Airway Hyperresponsiveness as an Additional Guide to Long-Term Treatment. *A .J Respir Crit Care Med.* 1999;**159**:1043.

137. Tomlin Z, Humphreys C, Rogers S. General practitioners'perceptions of effective health care. *BMJ* 1999;**318**:1532-5.

138. A C Freeman,.K Sweeney. Why general practitioners do not implement evidence: qualitative study. *BMJ* 2001;**323**:1100-3.

139. NHS Centre for Reviews and Dissemination University of York. Getting evidence into practice. Effective Health Care 5. 1999.