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Health Technology Assessment
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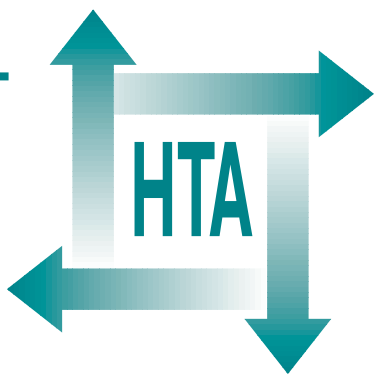

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The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Pharmaceutical Panel and funded as project number 93/14/09.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

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Contents

List of abbreviations

ASPEC	automated sample preparation with extraction columns
BDP	beclomethasone dipropionate
BGAM	British Guidelines on Asthma Management
BUA	broadband ultrasound attenuation
CAQ	Childhood Asthma Questionnaire
CUBA	Contact Ultrasound Bone Analyser
FEV_1	forced expired volume in 1 second
FRC	functional residual capacity
FVC	forced vital capacity
ICS	inhaled corticosteroids
LCI	Lung Clearance Index
MDI	metered-dose inhaler
PACQLQ	Paediatric Asthma Caregiver's Quality of Life Questionnaire
PEFR	peak expiratory flow rate
QoL	quality of life
RIP	respiratory inductance plethysmography
RR	respiratory rate
SD	standard deviation
SE	standard error
t_E	total expiratory time
t_{PTEF}	time from the onset of expiration to peak expiratory flow
VOS	velocity of sound

Executive summary

Objectives

- To establish recruitment rates of newly presenting asthmatic children.
- To establish acceptability of study protocols.
- To pilot age-specific quality of life (QoL) assessment.
- To assess short-term (6 months) outcomes of inhaled corticosteroids (ICS) treatment.
- To refine sample size calculations for a definitive study.

Design

A randomised pragmatic longitudinal trial design was used, with no blinding or placebo, to examine early ICS introduction similar to its use in practice. Subjects were assessed at entry, 3 and 6 months.

Setting

Subjects were recruited from six general practices. Children under 6 years were assessed at the Craig Research and Investigation Unit, Royal Aberdeen Children's Hospital, or their family home, and subjects 6 years and over were assessed at their general practice.

Subjects

Children (aged 6 months–16 years) with symptoms suggestive of asthma/wheeze that had commenced no longer than 12 months before were identified retrospectively and prospectively from general practices. Subjects were also required to be naïve to prophylactic therapy with no other lung disease/ concomitant illness.

Interventions

Subjects were randomised to β_2-agonist (β_2-only group) or β_2-agonist and ICS (ICS group) for 6 months. Physicians could later prescribe ICS in controls if needed.

Main outcome measures

- Pulmonary function
- Asthma symptom diary
- Symptomatic health status questionnaire
- Caregiver's and child's QoL
- Growth
- Bone mass
- Bone turnover
- Economic issues

Results

Of over 15,000 children yielded from general practice records, 11% had symptoms suggestive of asthma/wheeze, and two-thirds of these already used ICS. Of the remaining, 141 subjects met the criterion of early asthma, and 86 were randomised. Two-thirds of those randomised were < 6 years old, the males:females ratio was 2:1, and 67% had a family history of atopy.

Physiological development

Pulmonary function did not significantly improve in the older children. Although tidal breathing measures in the pre-school children were significantly higher at 6 months in the β_2-only group, there was great variability. Incidence of wheeze and night-time cough reduced equally in both groups. Reduction of night-time symptom score and reliever use, and increase in symptom-free days were only significant in the β_2-only group. No significant differences were found in growth and bone mass between the two groups, but bone metabolism was significantly reduced at 6 months in the ICS group.

Psychological development

The caregiver's QoL questionnaire was sensitive to child symptom changes over 3 months, but absolute impact of child symptoms on their QoL varied, whereas the child-centred questionnaire was not sensitive to change.

Economics

There were no significant differences in medical consultation costs between the groups, but, as expected, prescription costs in the ICS group were higher over 6 months. Combined healthcare

costs were significantly higher for patients assigned to ICS, but there were no significant differences in any effectiveness measures between the groups.

Conclusions

Most (96%) of the proposed sample was recruited, and the low drop-out rate (8%) demonstrated acceptability of the study protocol. Most children first presenting with symptoms suggestive of asthma were < 6 years old and represented a group biased towards mild to moderate asthma, or virally induced wheeze. The caregiver's QoL questionnaire was found to better reflect a child's symptom changes than a child-centred instrument. In the short term, no adverse effects were seen on growth, but ICS treatment significantly reduced bone metabolism. Most of the young children with asthma/wheeze improved over time with β_2-agonist treatment alone, and clinical benefits of early ICS intervention amongst these children were not detected; however, there was inadequate power in this pilot study to establish this. Calculation from the outcomes indicated a trial of 300 children would be required to determine treatment effects at 90% power.

Recommendations for future research

A larger definitive study is recommended, ideally only including children with asthma and not virally induced wheeze, to confirm the pilot study results, and investigate long-term effects and cost–benefits of early ICS use in newly presenting wheezing preschool children. In addition, it would be informative to determine the extent of ICS use in the total child population and any adverse effects of ICS on bone development that are separate from linear growth.

Chapter 1
Introduction

Rationale for the study

One of the research priorities of the 1995 NHS Health Technology Assessment (HTA) programme was whether, in adults and children who were newly diagnosed with asthma, very early introduction of inhaled corticosteroids (ICS) altered the long-term course of the disease, including prevention of irreversible airways obstruction. This was an extension of the practice, at that time, of introducing ICS when the disease was well established. The NHS HTA programme was concerned that very few studies had addressed the long-term outcome of different treatment strategies in asthma, and noted that this was of critical importance.

While ICS were the most effective treatment available, concerns persisted with regard to systemic steroid side-effects, particularly in children or when high doses were required. Although preliminary studies had indicated that ICS improved the quality of life (QoL) of the asthmatic patient, comparisons with alternative treatments were still needed.

Applications were invited for research projects that would determine whether early introduction of ICS in childhood asthma would:

(i) improve long-term outcomes
(ii) prevent progression of the disease
(iii) prevent irreversible airflow obstruction.

The proposed study had to consider QoL aspects, frequency of respiratory infections, frequency of hospitalisation and any adverse effects incurred through early introduction. The study also had to consider the pharmacoeconomics of long-term asthma therapy and examine both the direct and indirect costs of asthma. Due to the obvious methodological and ethical challenges that such a study would pose, the authority initially invited applications for feasibility studies.

This report presents the findings from one such study, the Early Asthma prophylaxis, natural history, Skeletal development and Economy (EASE) study. This was a 28-month pilot study performed by an Aberdeen Consortium made up of individuals from the University of Aberdeen, Grampian University Hospitals NHS Trust and the Rowett Research Unit, Aberdeen. The study was performed from February 1996 through to May 1998. It was proposed that a cohort of 90 newly presenting asthmatic/wheezing infants and children would be recruited from local general practices and randomised to receive ICS treatment for a period of 6 months. The study design incorporated a randomised pragmatic trial in which the positive and negative effects of ICS treatment would be studied over the whole span of childhood, in order to identify the separate effects of disease from those attributable to treatment, normal growth and maturation. Outcomes included: subjective health and QoL assessments; objective measures of lung function; linear growth; bone density and metabolism; consumption of health services; and cost–benefit of prophylactic compared to symptomatic treatment.

Background

Prevalence of childhood asthma

Asthma is the commonest chronic disease in Great Britain; it is suggested that about one in five children will have been given a diagnosis of asthma at some stage before they reach 15 years of age.[1] Asthma prevalence in childhood has risen substantially over the last 30 years. A key study in Aberdeen showed that about 4% of primary school children had asthma in 1964, but by 1989, this proportion had risen to 10%.[2] Over the same period, hay fever and eczema have also shown substantial rises in prevalence. These changes have been observed in other studies, most notably in Cardiff,[3] and are widely accepted as reflecting a real rise in prevalence and not simply a greater willingness of doctors to make the diagnosis.[4] The most recent survey in Aberdeen, in 1994, showed the prevalence in primary school children reporting a diagnosis of asthma to have risen to 20%,[5] while a study in the Highlands and Skye has found that 14% of children (17% in Skye) had asthma.[6] As asthma is incurable and often persists throughout the life of a patient, it is essential that it is controlled early so that its potential enormous health burden

may be reduced; in 1995 it was estimated that asthma consumed 2% of the UK health budget.

Asthma diagnosis

The term asthma is used in several different ways, either generally to describe any reversible airway obstruction or specifically to imply symptomatic atopic airway inflammation. It is also used to describe a particular episode of airway obstruction (wheezing), or to describe the tendency to develop recurrent episodes.[7] Correct diagnosis of the condition is, therefore, essential. The significance of early childhood wheezing illness associated only with clinical evidence of upper respiratory tract infection and its relationship to atopic asthma is unclear,[8–11] although there is increasing support for the view that childhood wheezing illness is a heterogeneous group of syndromes.[9] Whereas wheezing in infancy and early childhood appears to be associated with impaired small airway function rather than atopy, in later childhood atopy is a major determinant of wheezing illness.[12,13] It has been observed that the commonest pattern of wheeze in the pre-school population is predominately episodic wheeze associated with the clinical features of respiratory viral infection.[14] Evidence is also emerging for a possible third group associated with anatomically small airways present at birth as a consequence of intrauterine environmental factors and/or genetic predisposition.[15] It is not yet clear whether this group is at increased risk of developing atopic asthma or virally associated wheeze.[16] The implication of these observations needs to be taken into account in any early intervention studies as the optimal approach to treatment may differ between these different syndromes. It should be emphasised that some children's symptoms are not readily classifiable and that, within these three syndromes, there will be varying degrees of severity and frequency of attacks.

Current research is attempting to bring together recent molecular advances in the understanding of asthma with the epidemiological information available from well-characterised individuals and their families. In the future it may prove possible to provide a clearer genotypic definition of the different childhood wheezing syndromes. However, there are no useful predictors available to assign relative risks of persistence to individuals at first presentation. Studies of infants and young pre-school children[10,17,18] confirm clinical impressions that the presence or absence of response to common inhaled allergens are not good predictors of atopic sensitisation, but become more useful at 5–6 years of age, hence, the need for long-term follow-up in children diagnosed as asthmatic in infancy or early childhood.

Treatment of childhood asthma

The treatment of asthma has changed markedly over the last few years. With the recognition that asthma is a chronic inflammatory disease of the airways, there is now much earlier introduction of inhaled anti-inflammatory drugs, particularly ICS.[19] Clinical evidence shows that in children with 'classical' asthma, ICS reduce airway hyper-responsiveness, improve lung function and control background symptoms.[20] They also confer significant protection against exacerbations of asthma leading to hospitalisation.[21] A recent Swedish study found that despite an increase in the prevalence of childhood asthma, there was a decrease in hospital admissions due to acute asthma, suggesting that asthma is being well controlled in primary care.[22] A study of nearly 5000 Australian school children (aged 8–11 years) found that 13% were reported to be using ICS and/or cromoglycate.[23] Conversely, this study also found that 3% of the children were being under-treated. In contrast, there is little evidence to support the benefits of inhaled steroid use in children with viral episodic wheezing.[14,24]

The widely held view is that the use of ICS therapy is likely to increase following the 1997 publication of the British Guidelines on Asthma Management (BGAM).[25] The guidelines emphasise the importance of gaining control of asthma quickly, beginning with a moderately high dose of corticosteroid and then reducing the daily dose gradually. The aim is to adjust the treatment to the lowest dose required to maintain good control of asthma.

There are three ICS preparations currently available in the UK.

(i) Beclomethasone dipropionate (BDP) was the first to be introduced and has a maximum licensed dose of 400 µg daily in children. It is delivered via a pressurised metered-dose inhaler (MDI) or as a dry powder from breath-actuated devices. In young children, MDIs are used in conjunction with large volume spacing chambers.
(ii) Budesonide is also delivered by MDI (with or without spacer) and as a dry powder. Its maximum licensed dose in children is 800 µg daily, it can also be used as a nebulised solution (0.5–1.0 mg daily)

(iii) Fluticasone propionate is the most recently introduced steroid treatment and is, again, delivered by MDI (with or without spacer) and as a dry powder. It is unlicensed in children under 4 years of age and, because of its two-fold greater potency, is licensed in children over 4 years at a maximum dosage of half that of BDP, i.e. 200 µg daily.

It should be noted that the starting doses of ICS treatment recommended by the BGAM generally exceed the licensed doses.[25]

Safety of ICS use in childhood

Although there is clear evidence that early intervention with inhaled steroids may improve long-term outcome,[20,26] parents and healthcare professionals are concerned about systemic effects, particularly in growing children.[27–31]

Effects on growth

Evidence for significant side-effects of ICS are conflicting. Retrospective studies in Aberdeen have suggested that when asthma control is accounted for, the effects of ICS on linear growth are minimal.[27] These results contrast with other prospective studies, which suggest that growth is significantly decreased by ICS during childhood[32,33] and may recover when ICS is discontinued. There is also evidence that daily doses of BDP of less than 500 µg may cause suppression of the hypothalamic–pituitary–adrenal axis in some children.[34,35]

Short-term studies of linear growth have been assessed using knemometry,[36] a technique that is useful for showing acute effects of an intervention in infancy, but is less useful in older children, being a poor predictor of long-term growth. In a study of mildly asthmatic children of 6 to 13 years of age receiving 200–800 µg of budesonide daily for up to 18 days, a dose-dependent reduction in lower leg growth was observed when measured by knemometry.[37] Similarly, low doses of inhaled BDP have also resulted in a marked reduction in short-term lower leg growth in two studies in steroid and non-steroid dependent childhood asthma.[37,38] The relevance of short-term lower leg length is uncertain, as discussed above, but Doull and colleagues[32] have reported asthmatic children receiving low doses of ICS to be 0.8 cm shorter than a matched placebo group following 9 months of regular therapy. Tinkelman and co-workers[39] also noted that inhaled BDP caused growth velocity suppression when compared to theophylline in the long-term treatment of asthmatic children.

Growth velocity, particularly during mid to late childhood, is affected by the chronological age at which sexual maturation occurs. Although recent attention has focused on possible effects of ICS therapy on linear growth, the effects of asthma (or any chronic disease) on pubertal delay are well documented.[40] While it was first thought that persistent asthma could significantly reduce growth potential, longitudinal studies have confirmed that puberty is merely delayed and that target adult height is eventually achieved.[40] In any growth assessments during the pubertal period it is, therefore, essential to make some assessment of sexual maturity.

Effects on bone metabolism and bone density

Further studies, albeit in adults, have demonstrated small but significant effects on bone density which raise important questions on possible long-term effects on bone metabolism.[28] The relatively new quantitative ultrasonic measurement of bone has provided those working in the field of paediatrics with a relatively low cost, portable and, most importantly, radiation-free system for bone mass assessment.[41]

The potentially deleterious effects of steroid therapy on bone metabolism, primarily through inhibition of osteoblast function, are well recognised. In recent years, a number of improved biochemical markers that reflect the activity of bone cells during growth and metabolism have been developed. Based on fundamental research into the mechanisms of skeletal growth, the bone metabolism group at the Rowett Research Institute in Aberdeen has developed the pyridinium crosslinks of collagen, pyridinoline and deoxypyridinoline, as markers of bone resorption. Measurement of these compounds in urine provides a non-invasive technique for assessing changes in bone metabolism. These techniques have found wide application in adults for the diagnosis and monitoring of metabolic bone diseases,[42,43] and have been used to investigate systemic effects of ICS use in childhood.[44]

Effects on QoL

Although consensus has been achieved in the generation of guidelines for diagnosis and management of asthma,[25] there is now an ever-increasing awareness of the need for psychosocial, as well as biomedical, factors to be considered. Given the increasing prevalence, severity, and morbidity of paediatric asthma, the study of symptom perception may be a critical component in our understanding of asthma management, and will likely lead to usefulness of clinical

interventions.[45] Studies in adults have consistently shown only modest correlation between conventional clinical outcomes (e.g. airway calibre, symptoms, β_2-agonist use, etc.) and how patients feel and function in day-to-day activities.[46,47] The assessment of QoL is subject to a number of measurement difficulties, since it rests on the patient's or caregiver's perceptions. This means that measures are subjective and tend to be variable.

Recently, questionnaires have been developed to measure QoL for children with asthma.[48,49] The authors of these questionnaires have tested their reproducibility and concluded that children's QoL can be assessed reliably in response to changes in both clinical measures and the child's global perceptions of severity.[50] One of the problems for paediatric assessment is the fact that children represent a 'moving target' for measurement: their own abilities and attitudes may be changing rapidly due to normal development processes and, therefore, a QoL questionnaire's stability can only be viewed against this background. Cognitive developmental changes mean that the format of a child-completed questionnaire must be appropriate to the child's level of understanding.[51] Currently, two instruments have been developed to assess QoL in children. Juniper and co-workers[48] have developed an instrument to measure QoL in children of 7 years and older, whilst French and colleagues[49] have developed three questionnaire's, the Childhood Asthma Questionnaires (CAQs), which are suitable for children aged 4 to 7 (CAQA), aged 8 to 11 (CAQB) and aged 12 to 16 (CAQC) years. These instruments were developed for use during clinical drug trials where the scope for evaluating new medications was extended beyond the efficacy and safety issue into a QoL assessment.

Successful treatment of a child's asthma/wheeze should also achieve benefit for the family's broader QoL and functioning, as well as improvement in objective symptoms and clinical parameters. There is increasing interest in assessing these family QoL outcomes in clinical studies.[52–54] At least one controlled trial has found significant improvement in parental burden of care paralleling symptomatic improvement in children undergoing intervention.[55] Measures of perceived burden of care for parents may be as important as a child's self-report of QoL, because parental response to symptoms will play a part in the decision to seek medical care for the child. In adult asthma, it has been shown that QoL of patients, independent of symptom level,[56] predicts use of health services.[57] Currently, two measures of family burden of care exist. These are the Quality of Life of Parents of Asthmatic Children (QOL-PAC) scale developed by Schulz and colleagues[52] and the Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ).[54] The PACQLQ is designed to measure changes in family QoL. It measures the impact of child symptoms on family activity (CGAct) and parental anxiety and emotional response to the child's asthma (CGEmot), and gives a total score (CGTot) from the summation of the two subscales.[54] The PACQLQ was developed with parents of children aged over 7 years. It has been shown that, for this population, change in caregiver scores on the PACQLQ had moderate correlations with change in lung function, change in β_2-agonist use and clinical ratings of asthma control in the children studied.[54] However, use of the PACQLQ with parents of pre-school children with wheeze has not been reported.

Cost–benefits of early treatment

In terms of cost alone, anti-asthma medications are now among the most widely prescribed of all drugs in the NHS, accounting for 7% of all prescriptions in 1993. Asthma is one of the most frequent reasons for a general practice consultation and acute severe attacks of asthma are among the most common causes of emergency admission to hospital in children. It is commonly accepted that the financial costs of the illness are:

(i) direct medical expenditures
(ii) indirect costs.

Although persons with mild asthma incur low average annual costs associated with the illness, these estimates need to be viewed in the context of the large number of persons affected with mild asthma.[58] The annual cost of asthma to the NHS has been estimated at about £500 million. Indirect costs include morbidity from the disease in terms of time missed from work, being responsible for some 5.5 million days of sickness absence each year, at a cost of £350 million in lost productivity and £60 million in benefits. For children the hidden costs are substantial and include time lost to work by a parent during periods of illness and, for children of school age, time lost from schooling. Although health benefits are often assessed by placing a monetary value to these benefits, reduced disruption to schooling provides less scope for the placement of a monetary value. Therefore, to evaluate the cost-effectiveness of

different asthma therapies, measures of cost-effectiveness are necessary, for example:

(i) incremental cost per unit improvement in lung function
(ii) incremental cost per avoided day of absenteeism from school
(iii) incremental cost per symptom-free day gained.

Although childhood asthma has been reported by us to result in increased absences from school and work, the long-term outcome in socio-economic terms has nevertheless been favourable.[59] These data relate to asthma in the 1960s and 1970s when the employment market was very different and may not be applicable at the start of the twenty first century. Although the use of inhaled steroids may be cost-effective now, the cost could be enormous in the long term. For example, they may increase the risk of osteoporosis.[60] Therefore, there is a need for long-term studies of bone mass development in asthmatic children on ICS treatment. Careful long-term study is needed because factors other than inhaled steroid treatment may influence the natural history of osteoporosis.[60]

Economic question

The central economic question is whether or not it is worth incurring the additional costs of early asthma prophylaxis. The benefits of 'successful' prophylaxis would come in two forms: reduced future healthcare utilisation and improved health. The former is best treated on the cost side and, thus, the net cost of early asthma prophylaxis to the NHS should be estimated taking into account savings as a result of reduced future utilisation. If the net cost is negative (savings exceed the cost of prophylaxis) the intervention is desirable, so long as it does not have any negative impact on the health of patients. If there is a net cost to prophylaxis, this must be compared with any health benefits.

A comparison of the net costs and the health benefits of prophylaxis would be assisted if a monetary value could be placed on these benefits. However, because the intervention is aimed at children the benefits of better-managed asthma may be, in part, reduced disruption to schooling rather than in terms of increased labour market productivity, and thus there is less scope for placing a monetary value on them. Also, in the case of the improved management of childhood asthma, one important group of beneficiaries are the parents (or guardians) of the children. While it is possible to identify cost savings to these individuals as a result of better controlled childhood asthma (fewer general practitioner (GP) visits, etc.), such a measure is likely to be a highly imperfect estimate of the benefit to them of improved asthma management. A more satisfactory alternative may be to use contingent valuation methods to value the benefits to parents of improved asthma management for their children.

The alternative to undertaking a cost–benefit analysis is to perform cost-effectiveness analysis. This involves estimating the cost per unit of outcome achievable through early asthma prophylaxis. Such measures can then be compared with similar measures for other interventions aimed at improving asthma management. While such an analysis cannot demonstrate that a particular intervention is worthwhile, it can indicate the relative cost-effectiveness of a number of different interventions with a common outcome.

Long-term outcomes of drug use in asthma

Despite a greater awareness of the disease and improved treatment, asthma remains the most important chronic disease of childhood. Although, in the future, modification of the child's early environment may reduce the disease prevalence,[61] at present it is appropriate to concentrate on starting therapy as early as possible. It has been found that a large number of asthmatic children are already being managed with long-term ICS.[22,23] These numbers are likely to increase as more GPs implement the new guidelines on asthma management.[25] This further emphasises the need to monitor the long-term risks, costs and benefits of very early introduction of ICS.

Trial design – explanatory versus pragmatic

Healthcare interventions are either explanatory or pragmatic. The distinctions between the two types of trial are that the former tests a biological hypothesis whilst the latter provides evidence to permit a choice between alternative treatment policies. Explanatory trials usually precede pragmatic trials and are designed to look at the mechanisms by which interventions may produce an effect, frequently including laboratory-based outcome measures. In contrast, pragmatic trials tend to involve larger populations, and are designed to more closely simulate normal practice by use of familiar clinical outcomes. In general, where explanatory and pragmatic aims conflict, the pragmatic aim will take priority as the latter design maps more closely onto 'real life' practice.[62]

There is much literature discussing both the merits of the two trial designs[62,63] and the presentation of results from pragmatic trials.[64–69]

In brief, explanatory trials generally assess efficacy, whereas pragmatic trials assess effectiveness. Most surgical interventions are assessed using pragmatic trial designs, but this approach is equally valid for medical interventions. The primary aim of the explanatory approach is to further scientific knowledge and is a requirement for the licensing of new therapeutic agents. In contrast, the pragmatic trial design reflects variations between patients that occur in real clinical practice and aims to inform choices between treatments. The pragmatic approach has become increasingly more important to the purchasers and providers of healthcare because they can use the evidence from pragmatic trials to make policy decisions. The pragmatic trial can be, but is not usually, blinded and seldom uses placebos, however, this is not seen as detrimental because the physicians' and patients' responses to treatment are an accepted part of the overall assessment and reflect the likely clinical response in practice. The outcome measures in explanatory trials often relate to understanding the biological basis of the response to treatment. In pragmatic trials, outcomes represent the full range of health gains, for example, both physiological and psychological responses to treatment. The two approaches will not always produce the same conclusions with regard to benefit of treatment, either because a treatment which works in an ideal setting does not work in real life or because improvement in a biomedical endpoint (e.g. peak expiratory flow rate (PEFR)) does not produce the expected health gain.

Research questions

The objective of a definitive trial should be to establish whether early introduction of ICS has a significant effect on the subsequent course of wheezing illness in children. Any benefit of the early introduction would have to be examined alongside any possible negative effects.
A definitive trial should establish:

(i) the impact of early ICS prophylaxis on wheezing illness presenting at different stages over the whole period of growth and development
(ii) the effects on growth
(iii) the effects on bone metabolism and bone density
(iv) the effect on QoL and illness behaviour
(v) the cost–benefit of early treatment.

The objectives of the EASE pilot study, presented in this report, were:

(i) to establish recruitment rates within a well-defined region
(ii) to establish acceptability of protocols
(iii) to pilot age-specific QoL assessment
(iv) to assess the short-term (6 months) outcomes of ICS treatment
(v) to refine sample size calculations for a definitive study.

The pilot study could not answer the cost–benefits question, but rather provided an opportunity to collect economic information, which would be of benefit to the design of a definitive study of the cost-effectiveness of early asthma prophylaxis.

The health economic component of the pilot study had four aims:

(i) to provide an estimate of the overall cost-effectiveness
(ii) to identify the best means of data capture for the economic aspects for use in any further study
(iii) to inform decisions with respect to sample size in any further study
(iv) to ensure that there are suitable outcome measures available with which to assess cost-effectiveness in any further study.

Chapter 2

Study design, subjects and methods

Ethical approval for the project was granted by the Joint Ethical Committee of Grampian Health Board and University of Aberdeen (Project number: 2464). Permission for the study was also granted by the Grampian Area General Practice Subcommittee.

Setting

Children under the age of 6 years were assessed in the Craig Research and Investigation Unit, Royal Aberdeen Children's Hospital, Foresterhill, Aberdeen. Subjects 6 years of age and over were assessed at their general practice surgery. Some assessments in those under 6 years of age were carried out at the subject's family home.

Recruitment

General practice

Once the Grampian Area General Practice Subcommittee had approved the study protocol, nine general practices within a 40-mile radius of Aberdeen were approached and invited to participate in the study. Initially, a copy of the study rationale (appendices 1 and 2) was sent to all practice partners, and this was followed up by an informal presentation of the study protocol to the practice staff. Six general practices agreed to participate in the study that reflected the urban/rural mix of the region. The participating practices were:

1. Elmbank Group Practice, Foresterhill Health Centre, Aberdeen (urban)
2. Northfield–Mastrick Medical Practice, Aberdeen (urban)
3. Scotstown Medical Practice, Aberdeen (urban)
4. Peterhead Health Centre, Peterhead (rural)
5. Inverurie Medical Group, Inverurie (rural)
6. Portlethen Health Centre, Portlethen (rural).

Subjects

Eligible infants and children were identified both retrospectively and prospectively from general practices. The entry criteria for subjects were:

(i) aged between 6 months and 16 years
(ii) a history suggestive of asthma and/or recurrent wheeze (i.e. at least two episodes of wheezing)
(iii) symptoms which had commenced no longer than 12 months prior to consultation
(iv) naïve to prior prophylactic therapy
(v) no other lung disease or concomitant illness.

Once a general practice was recruited, their computerised records were searched for eligible subjects (aged 6 months to 16 years) using two separate search criteria: a diagnosis of asthma and a repeat prescription for β_2-agonist. These searches were repeated monthly for the duration of the study. In addition, throughout the study, practice staff supplied names of new patients attending practice asthma clinics. The resultant names produced by these searches then had their practice records studied by a member of the study team. If all eligibility criteria were met, subject's parents were sent a copy of the study information sheet (appendix 3) with an accompanying letter of introduction from their GP. This was followed up, some days later, with a telephone call from one of the study staff. If the family agreed to participate, an initial appointment was booked for them. Subject and/or parental written informed consent (appendix 4) was obtained at this initial appointment, which represented study entry.

Study design

Design

The study used a randomised pragmatic longitudinal trial design. The study tested a policy of early introduction of ICS similar to the way it would be used in practice. There was no blinding and no placebo, although the primary care physician could subsequently prescribe ICS in the control group if a clear indication developed, in keeping with national guidelines.[25] Once identified as asthmatic and/or wheezing, children and infants were treated with β_2-agonist, in accordance with step 1 of the BGAM.[25] After consent was obtained the infant or child was then randomised to one of two groups:

(i) β_2-agonist for 6 months (β_2-only group)
(ii) β_2-agonist and ICS for 6 months (ICS group).

Subjects were assessed on trial entry and reassessed 3 and 6 months later. Once randomised, the family doctor was contacted and informed as to which treatment their patient had been allocated, and if ICS were required, the GP was asked to prescribe them (appendix 5).

Randomisation

A stratified computerised random allocation (using a programme designed by Health Services Research Unit, University of Aberdeen, Department of Public Health, Foresterhill, Aberdeen, incorporating Microsoft Access) was made prior to the initial visit and the results were stored in a sealed envelope (appendix 6). The envelope seal was only broken if informed consent was obtained. If consent was not obtained, the envelope was destroyed and the subject's name removed from the computerised database. Randomisation was stratified on age, sex and general practice to ensure balance in these key prognostic variables. Three age cohorts were used; 0.5 to < 6 years, 6 to < 10 years and 10 to < 16 years. At the end of the 6-month treatment period, the GPs were re-contacted and advised to reassess their patients (appendix 5) following BGAM.[25] It should be noted that GPs could alter the treatment during the first 6 months if current therapy was judged to be failing to control symptoms.

Sample size

Short-term studies of asthmatic children have shown improvements in lung function (forced expired volume in 1 second (FEV_1)) with ICS which parallel the increase in twice daily peak expiratory flow meter (PEFR) records performed in the home.[70] The mean improvement over 2 weeks in FEV_1 of 8%, from 1.67 to 1.82 litres, was similar to the 6–8% difference found in untreated wheezy children when compared to symptomatic children treated with rescue or rescue and prophylactic therapy in an American study.[71] Hence, we sought to detect a 7% difference in the growth rate of FEV_1 between the prophylactic and symptomatically treated group. For a difference to be detected at the 5% level with an 80% power would require just over 30 individuals per treatment group.[72] Although the pilot was not planned as a definitive study, we sought to recruit 30 children in each of the three age cohorts, 90 in total, in order to provide 60 children above the age of 6 years with full spirometry available. Thirty children in each of the age groups should also provide adequate numbers for any obvious age effects of the intervention.

Asthma treatment

The brand name of ICS and the exact delivery device was left to the discretion of the GP, although clear guidance was provided as to age-appropriate delivery devices, such as a spacer (with or without facemask) or a dry powder inhaler. The dosage prescribed was within the range recommended in the appropriate data sheets and the British National Formulary. These data were summarised for the convenience of the GP prescriber and were either 200 µg BDP/budesonide twice daily or 100 µg fluticasone twice daily.

Compliance

Compliance to ICS treatment was assessed as the number of prescriptions recorded in the children's primary care practice records related to the number of prescriptions required to complete 6 months of treatment. Compliance to β_2-agonists was not assessed as these were used on an as-required basis only.

Anthropometry

Anthropometry was conducted in accordance with the guidelines provided by Tanner and Whitehouse.[73] Subjects were fully accustomed to the experimental procedures prior to measuring sessions. All staff were trained in the Growth Clinic at the Royal Aberdeen Children's Hospital.

Chronological age

Age of the subject was recorded to the nearest 0.01 year (appendix 6) by subtracting the decimal year of the subject's date of birth from the decimal year of the day of the test.[73]

Stature

Standing height was measured to the nearest millimetre with a Harpenden stadiometer (Holtain Ltd, Crosswell, UK). The subject stood with their back and heels in contact with the vertical surface of the stadiometer. The head was held so that the child was looking straight forwards with the lower borders of the eye sockets in the same horizontal plane as the external auditory meati. A right-angled counter-weighted block was then slid down until its lower surface touched the child's head, and the scale was read to the nearest complete millimetre.[73] The measurement was performed twice and averaged, and this result was used in all analyses (appendix 6). (See appendix 7 for calibration procedure.)

Body mass
Body mass was measured to the nearest 100 g on either electronic or sliding weight scales (appendix 6).

Knemometry
Knemometry, a measure of knee to heel length, has been established as an integral part of the available measures of short-term systemic activity of steroids in children.[37] Knemometry was assessed using a hand-held trigger-activated portable knemometer (Biomedical Physics Department, University of Aberdeen, Foresterhill, Aberdeen). In addition to the three visits to the testing centre, measurements were also taken at home weekly for four consecutive weeks after the subjects' initial assessment. Where possible, the same individual carried out these measurements using the following protocol:

(i) same time of day
(ii) child lying on their back, with lower leg clothing removed
(iii) right leg
(iv) footplate position the same for all measurements
(v) five measurements with a standard deviation (SD) of less than 0.8 mm.

The mean knee–heel length from five measurements was recorded along with the SD of the measurement (appendix 6).

Sexual maturation

External maturity was visually assessed using indices of secondary sexual characteristics development.[74] Stages of genitalia and breast development, and of pubic hair development were recorded using a standard rating of 1 to 5. Stages of axillary hair development were recorded using a standard rating of 1 to 3 (appendix 6).

Menarche
Female subjects were also questioned as to whether menarche had occurred (yes or no), and, if it had, the date of the first menstrual period was recorded (appendix 6). The mother's age of menarche was also recorded (appendix 8).

Pulmonary function

Spirometry
Dynamic lung volumes and forced ventilatory flow rates were recorded using a 2120 hand-held storage spirometer (Vitalograph Ltd, Maid's Moreton House, Buckingham, UK) interfaced with a Toshiba Portable Personal Computer (T2110CS), using Spirotrac software (Vitalograph Ltd, Maid's Moreton House, Buckingham, UK). Measurements were performed with the subject in a standing position. Subjects were encouraged to produce their greatest possible effort, and further encouragement was provided by the software's incentive display. Judgement about the technical quality of forced manoeuvres was made using the following standard criteria:[75]

(i) the FEV_1 and forced vital capacity (FVC) were taken as the highest values from the first three technically satisfactory forced expirations
(ii) the FVC value chosen did not exceed the next highest by more than 0.3 litre (appendix 6). Volumes were expressed in litres and flows in litres/second at atmospheric conditions of body temperature, ambient barometric pressure and saturated with water. (See appendix 7 for calibration procedure.)

During the forced manoeuvre, two flow rate measures were also recorded: PEFR and flow rate at 50% FVC.

Lung function in pre-school children
Although the assessments of lung function and, in particular, airway function are well established in children and adolescents of school age, other assessment techniques are required for the younger population. For frequent measurements in a large number of infants, tidal breathing parameters, using either surface bands or a mask and a pneumotachograph, may be more appropriate.[76–78] There are conflicting reports of the ability of such tidal measurements to discriminate between groups of infants,[77,79] or to identify response to intervention.[80] However, in population studies, the measurements appear to discriminate between the extremes of respiratory development.[76,81,82]

Lung volume measurements
Functional residual capacity (FRC) was determined by the open-circuit nitrogen washout technique.[83] If the amount of nitrogen washed out is measured and the initial alveolar nitrogen concentration is known, then the lung volume at which the washout was initiated can be calculated.

$$FRC = \frac{\text{volume of nitrogen washed out}}{\text{initial lung nitrogen concentration}}$$

Measurements were performed with the child in a seated position. Tidal breathing parameters were recorded with the child breathing normally through a facemask, which had a pneumotachograph and three-way valve attached to it. Initially, the child was breathing air from the room, and then the child was switched to inspire 100% oxygen. The nitrogen sample tube was attached to the three-way valve and a nitrogen analyser. The volume of nitrogen exhaled was determined by integrating, over time, the product of flow and nitrogen concentration. Flow was measured using the pneumotachograph, and variations in gas temperature, composition and viscosity were also recorded, as well as the phase shift between the flow and nitrogen concentration signals. The Lung Clearance Index (LCI), based on the efficiency of nitrogen clearance during the washout procedure, was determined concurrently with FRC (appendix 6).

Tidal breathing parameters

Tidal breathing pattern analysis was used to assess airflow obstruction.[82] Tidal breathing parameters were obtained by placing respiratory inductance plethysmography (RIP) bands on the child's chest and abdomen over their clothes. One band was placed around the chest at the nipple line and another around the abdomen at the level of the umbilicus, and these were fastened with poppers. If the child's clothing was too loose-fitting, the top layer of clothing was removed and the two bands were placed over the child's vest in order to minimise interference with the signal. The child was encouraged to sit very still, while watching a video, as whole body movements are known to affect the signal. Tidal breathing data was recorded during 5 minutes of quiet breathing. Tidal breathing analysis, from the summed chest and abdominal signals, was used to obtain respiratory rate (RR). Time from the onset of expiration to peak expiratory flow (t_{PTEF}) and total expiratory time (t_E) were derived from the differentiated summed signal. Results are presented as a ratio of t_{PTEF}:t_E, the mean value of t_{PTEF}:t_E calculated from a minimum of 10 and a maximum of 40 breaths (appendix 6).

Bone mass

Quantitative ultrasound of the left os calcis was measured using a Contact Ultrasound Bone Analyser (CUBA) fitted with paediatric transducers (McCue Ultrasonics Plc, Winchester, UK). The CUBA system was interfaced with a Toshiba Portable Personal Computer (T2110CS), using CUBA Clinical V3 software (McCue Ultrasonics Plc, Winchester, UK). Two parameters were assessed: broadband ultrasound attenuation (BUA) and velocity of sound (VOS), expressed in db/MHz and m/second, respectively. Whilst BUA and VOS do not truly measure bone mineral density, they have been shown to predict bone density of the calcaneaum and have the advantage of being a radiation-free method.[84] Subjects were seated and the anterior–posterior length of the foot was measured, and, if necessary, a footplate was placed in the footwell of the CUBA. Subjects then placed their left foot into the footwell and two ultrasonic transducers were positioned either side of the calcaneaum. The transducers were coupled to the heel using an ultrasonic coupling gel. BUA and VOS measurements were repeated three times (the CUBA took a minimum of three scans in succession for each measurement), and the calcaneaum was repositioned between each measurement. The average of these three measurements was recorded for analysis (appendix 6). (See appendix 7 for calibration procedure.)

Bone metabolism

Whenever possible, overnight timed urine collections were made, on the night prior to assessment, for collagen crosslink analysis. Pyridinoline and deoxypyridinoline are crosslinks in type I collagen, which is the predominant type in bone. Both crosslink products are not metabolised in the body, and thereby provide an estimate of bone resorption.[42,43] Any changes in growth should thus be seen as a change in the proportions of crosslinks excreted, with an increase associated with accelerating skeletal growth and a decrease with reduced growth. If overnight collections were not possible, evening and morning spot urine samples were collected. Instructions and materials were mailed to subjects' parents in the week prior to assessment (appendix 6).

Overnight urine

Subjects were instructed to empty their bladder prior to going to bed and to note the time. A sample of this urine was then stored and the remainder discarded. All urine passed overnight was then collected and stored in a separate container. In the morning all urine passed immediately on rising was collected and added to any overnight urine collected and the time of collection noted. This sample was than stored in a cool place and brought to the assessment centre within 10 hours. At the centre,

the volume was recorded, a sample taken and the remainder discarded.

Spot urine

Infant spot urine samples were collected by placing cotton wool balls into the last nappy of the day. The wet cotton balls were then placed in a container and stored in a cool place overnight. At the assessment centre, the cotton wool balls were placed in a syringe and a sample squeezed out. Infant samples were also collected in the same way during the assessment visits. In older children, spot samples were collected in the evening and morning prior to assessment visits. Any samples with faecal contamination were discarded.

Urine analysis

All urine samples were frozen and stored at –20°C until they were analysed in the Rowett Institute Bone Metabolism Unit, Aberdeen. Analysis of full collections (all samples collected over 6 months) reduced the potential effects of inter-assay variations. Pyridinoline and deoxypyridinoline were assayed by a fully automated technique using ion-pair reversed-phase high pressure liquid chromatography on urine hydrolysates.[85] Urine was first hydrolysed with hydrochloric acid to free the crosslinks. After centrifugation, a small amount of supernatant was transferred to automated sample preparation with extraction columns (ASPEC) sample tubes. A synthetic pyridinoline analogue was used as an internal standard enabling quantification of crosslinks. Samples were injected from ASPEC into the high-performance liquid chromatographer and a chromatograph produced from which pyridinoline and deoxypyridinoline concentrations were calculated. Values were corrected for urinary creatinine concentration.

Self-report measures

Diary card

Connolly and Godfrey[86] first developed subjective outcome variables for efficiency of treatment in asthma. This diary card, which is widely used for asthma trials, has stood the test of time, and although attempts have been made to improve on this approach by including more objective measurements, such as peak expiratory airflow variability[87] and recording of nocturnal cough,[88,89] the symptom-reporting technique still remains the basis of assessment, particularly in young children. Despite the criticism of diary card approaches in asthma and the use of short-term retrospective questionnaires,[90] the fact that identification of childhood symptoms predicts outcome over 25 years later[11,91] and that lung function measures of airway obstruction, including FEV_1 and maximal mid-expiratory flow, have been found to be reduced in individuals identified by such techniques[71] suggests that parental reporting or self-reporting of symptoms are reliable. Two 31-day diary and event cards were completed prior to assessments two and three.[90,92] The diary-recorded daily daytime and night-time symptom scores are shown in *Box 1*.

BOX 1 Diary-recorded daily daytime and night-time symptom scores

Night-time symptoms

0	No symptoms during night
1	Symptoms on waking but not causing your child to wake early
2	Symptoms causing your child to wake once or to wake early
3	Symptoms causing your child to wake twice or more (including waking early)
4	Symptoms causing your child to be awake most of the night
5	Symptoms so severe that your child did not sleep at all

Daytime symptoms

0	No symptoms during the day
1	Symptoms for one short period during the day
2	Symptoms for two or more short periods during the day
3	Symptoms for most of the day which did not interfere with usual daytime activities
4	Symptoms for most of the day which did interfere with usual daytime activities
5	Symptoms so severe that your child could not perform their usual daytime activities

A month symptom score was obtained by summing scores for each day and night, giving a possible range of 0 to 310 per child per month. The number of symptom-free days (giving a score of 0 to 31) was also calculated. The diary also recorded night-time and daytime use of reliever inhaler; days off school/playschool/nursery due to symptoms; visits to the GP; and visits to hospital accident and emergency clinics.

Health status and family history

On entry to the study, a standardised questionnaire[91,93,94] was used to obtain information from parents (appendix 8). It included questions on the child's birth details; history of wheeze; treatments used; other atopic diseases;

exposure to smoke and pets in the family home; family history of asthma and atopic disease; and asthma history of siblings. A modified version of the questionnaire was used at subsequent visits to assess history of wheeze and treatment used (appendix 8: questions 1–6, 9 and 10). Socio-economic status of the families was assessed by Carstairs deprivation score from the family home's postal code.[95] These are derived from locality indices using census data for over-crowding, male unemployment, low social class, and no car as variables and have been shown to relate to health outcomes. They range from 1 (best: affluent) to 7 (worst: deprived).[96–98]

QoL

For children with a chronic problem such as asthma, the expectation of encountering a range of somatic and psychological symptoms could influence perception of disability and handicap. The different ways in which people respond to the effects of disease have been described as 'illness behaviour'. Such behaviours determine the extent to which illness interferes with usual life routines and the uptake of healthcare. Important measures of outcome include consumption of health resources, use of rescue medications, and behaviours such as staying away from school or reducing activity in sports. However, many of these behaviours are influenced by health beliefs and perceived vulnerability to the disease, which need to be accounted for. It is likely that improved control of symptoms will, by experiential behaviour, modify the perception of vulnerability in affected individuals.[46–50,54] To address these issues, we used two measures of QoL.

Caregivers' QoL

Parents and primary caregivers of children with asthma are limited in normal daily activities and experience anxieties and fears due to the child's illness. The PACQLQ was developed to measure these impairments and was used in the present study. It measures the impact of child symptoms on family activity (CGAct) and parental anxiety (CGEmot). All PACQLQ total (CGTot) and subscale (CGAct, CGEmot) scores can range from 1 (worst) to 7 (best). Although this instrument has been validated in children above 7 years of age, no reports are available describing its use in the parents of younger symptomatic children. We, therefore, sought to assess the performance of this instrument in the parents of young symptomatic children in the setting of a clinical asthma trial. The issues we sought to address were the relationship (if any) between symptom reporting and perceived parental QoL, and whether any obvious parental attributes modified these relationships.

Child's QoL

Optimal management of asthma increasingly requires children to take some responsibility for self-management. It is, therefore, essential to understand how they view the disorder, and to explore their perceptions of 'QoL'.[49] French and Christie[49,50] have developed such a questionnaire and this was used in the present study. There are three forms of the CAQ: form A (CAQA), for children of 4 to 7 years of age, requires parents to help their child respond to picture stimuli; form B (CAQB) for 8 to 11 year old children uses the same picture stimuli but with text suitable for independent reading; and form C (CAQC) for children aged 12 to 16 years uses a more advanced system of the same response format. The scoring recorded from the forms is shown in *Box 2*. We sought to address the issues of the feasibility of using the questionnaire in these children, and whether there was a relationship between symptom reporting and child-centred QoL.

Economic issues

It was not only important to identify the costs to the NHS, but also the costs falling on the families of affected children. Information was obtained from the patients' general practice notes and from the 31-day asthma diaries. The total number

BOX 2 The scoring recorded from the CAQ forms

CAQA	
Quality of living score	10 (low) to 40 (high)
Distress score	4 (low) to 15 (high)
CAQB	
Active quality of living score	7 (low) to 35 (high)
Passive quality of living score	4 (low) to 20 (high)
Distress score	6 (low) to 30 (high)
Severity score	6 (low) to 23 (high)
CAQC	
Active quality of living score	8 (low) to 36 (high)
Teenage quality of living score	5 (low) to 23 (high)
Distress score	12 (low) to 60 (high)
Severity score	9 (low) to 45 (high)
Reactivity score	5 (low) to 24 (high)

of prescriptions recorded during the trial was collected, along with information with regard to number of GP and hospital visits and any specific tests requested by the GP (appendix 6).

Three measures of cost-effectiveness were considered:

(i) incremental cost per unit improvement in lung function
(ii) incremental cost per avoided day of absenteeism
(iii) incremental cost per 'symptom-free' day gained.

These measures are useful for making comparative statements regarding the cost-effectiveness of different asthma therapies for children, but provide less insight if the comparison is with other forms of healthcare spending. This would require the calculation of measures such as the cost per quality-adjusted life-year saved. However, such measures are likely to be problematic in the context of the present study. Given the relatively small sample size and short time horizon, it was considered unlikely that such measures would be sensitive enough to distinguish between therapies. There is, in any case, very limited experience with suitable QoL measures in a young population.

The net costs of prophylaxis to the NHS could readily be estimated, at least in the short term, by comparing the healthcare utilisation of the early prophylaxis and control arms. However, the identification of the relationship between differences in cost observed during the follow-up period and the eventual differences in lifetime costs would prove harder to identify. Since the overall attractiveness of early prophylaxis would depend not only on the size of any initial cost savings but also on how long they would last, it would be necessary to model the future cost differences under a range of assumptions. We proposed to test these assumptions as the data became available. Since a pilot study would be unlikely to involve a sufficiently long follow-up of patients, predictions of the longer-term resource implications would have to be based on short-term study data and any other relevant sources of information. We considered it important that the timing of the net costs of asthma prophylaxis should be considered. For example, in order to generate future savings, it may be necessary to incur higher costs in the short term. The timing of any net costs or net savings could, for example, be taken into account by use of an appropriate discount rate; we used a figure of 6% per annum.

In order to identify the net costs of prophylaxis, the following information was collected for each patient from their medical records for the 6 months following entry into the trial: prescriptions; GP consultations (asthma- and non-asthma-related); outpatient visits; and inpatient stays. The costs of prescriptions were calculated using cost information from the 1997 British National Formulary. GP consultations were recorded according to the type of consultation. The cost of GP consultations can be approximated using national estimates, and it has been estimated that the cost of a surgery consultation, in 1997, was £9, a home visit £27 and a consultation with a practice nurse £6.

Information was also collected to assess whether there were any differences in effectiveness between the two arms. Three measures of effectiveness were considered: symptom-free days; lung function measures, including spirometry and tidal breathing parameters (t_{PTEF}:t_E); and health-related absenteeism from school. Symptom-free days and absenteeism were assessed via patient-completed health diaries.

Data processing

Data were stored in ACCESS 97 database management system (Microsoft Corporation, USA). Two tables were used (one for single measurement data and the other for repeated measurement data) and tables were linked by study number. In total, each subject had a maximum of seven rows of data, one for each measurement visit. Data were exported from ACCESS and then imported and saved as SPSS files (SPSS version 7.5.2, SPSS Inc, Chicago, Illinois, USA). SPSS data files were then merged where appropriate.

The quality control of longitudinal data is critical since within-individual differences are generally subtler than differences between groups. Data entry into ACCESS 97 was continuous throughout the study and was then double-checked on completion.

Statistical analysis

All analyses used the intention-to-treat principle. As this was a pilot study (with small populations), no assessments were made between the different types of inhaled steroid or delivery devices. Thus, class effect of ICS, rather than intraclass differences, were assessed.

Descriptive statistics (means, medians, minimums, maximums, SDs and standard errors (SEs)) were applied to all variables. Statistical comparisons between treatment groups were performed using independent samples *t* test and Kruskal–Wallis test as appropriate. Comparisons between repeated measures were performed using paired samples *t* test and Wilcoxon two-related-samples *Z* test. Secondary analysis included simple factorial analysis of variance models (SPSS version 7.5.2, SPSS Inc, Chicago, Illinois, USA). When it was appropriate to obtain maximal use of all the longitudinal data available, a multilevel modelling approach[99] was used (MlwiN, Multilevel Models Project, Institute of Education, University of London, UK).[100]

In brief, multilevel modelling is an extension of ordinary multiple regression where the data have a hierarchical or clustered structure. In this context, a hierarchy consists of units or measurements grouped at different levels. When individuals are measured on more than one occasion, the occasions are clustered within individuals, who represent level-2 units, with the measurement occasions being level-1 units. The models yield estimates of the average response variable related to other coefficients. Using this type of modelling coefficients at one level of the hierarchical system can be viewed as variables that also function at the second level. In addition, coefficients of within-individual variation are generally estimated better than they would be if a single-level analysis was conducted for each group.[99] However, the main focus of multilevel analysis is not the individual subject, but the estimation of variation in all subjects, i.e. to examine group differences. When this is done, it is possible to estimate the independent effects that other characteristics have on the response variable.

Chapter 3
Results

Recruitment

The trial was performed in three urban and three mixed urban/rural general practices. In total, there were 15,036 infants and children (< 16 years of age) registered with these six practices. They represented 18% of the total child population (< 16 years of age) in Aberdeen City and Aberdeenshire. Of the population under study, 11% had recurrent symptoms suggestive of asthma (*Table 1*), with individual practice percentages ranging from 5.9 to 14.4%. Nearly two-thirds (63%) of these symptomatic children were being prescribed ICS in combination with β_2-agonist; practice percentages ranged from 26 to 93%. In total, 1022 children (7%) of the total child population under study were being treated with ICS in combination with β_2-agonist. Children (n = 146) who fulfilled the entry criteria were approached to participate in the study, and 86 (59%) agreed to participate (*Figure 1*).

The majority of those recruited were under 6 years of age (76%) and 66% were male (*Figure 2*). There was no statistically significant difference in social deprivation scores[95] (1 = high, 7 = low) in those in whom the score could be derived, between those who were recruited (n = 75, median 2, range 1–7), and those who declined to participate (n = 51, median 2, range 1–7) ($p > 0.05$). Of the 55 who declined, 19 (34 %) did so due to concerns with regard to steroid safety, whilst another third stated they were too busy to participate. The study was completed by 79 children (92%); two withdrew because the family moved out of the area, and the remainder withdrew because parents were unable to attend reassessment visits. There was no evidence that these children differed in any way from the other participants.

Treatment

The preparations prescribed in the ICS group were BDP (n = 27) and budesonide (n = 17); fluticasone was not prescribed. In the majority of cases (n = 30; 68%), a spacer and MDI was used to deliver the drug. Only six (14%) used a dry powder inhaler, six (14%) used a breath-activated inhaler, and two (4%) used an MDI. Ten children in the β_2-only group were later prescribed ICS (at an average of 58 days from randomisation, range 8 to 146 days) and four in the ICS group had ICS doses increased (*Figure 1*).

Compliance

Compliance was assessed in 40 of the 44 (91%) children randomised to ICS therapy. We were unable to assess compliance in four cases due to a lack of documented evidence of prescribed treatment in the child's primary care record. Compliance, assessed as prescriptions recorded as a percentage of those required to complete 6 months of treatment, ranged from 25–150% (median 50%); 31 (77%) had a compliance of 50% or above, and 16 (40%) had a compliance of 75% or above. A compliance of more than 100% was likely to reflect lost or duplicated prescriptions indicating that treatment was available both at home and school.

TABLE 1 *Distribution of child population in six GP practices, incidence of wheeze and treatment*

	General practice							
	1	**2**	**3**	**4**	**5**	**6**	**Total**	**% Child population**
Child population (6 months–16 years)	1782	4630	922	3036	1248	3418	15,036	
Recurrent cough/wheeze	195	273	101	436	171	441	1617	11%
Repeat prescription of inhaled steroid and β_2-agonist	147	191	26	159	89	410	1022	7%
Repeat prescription of β_2-agonist alone	48	82	75	277	71	31	584	4%

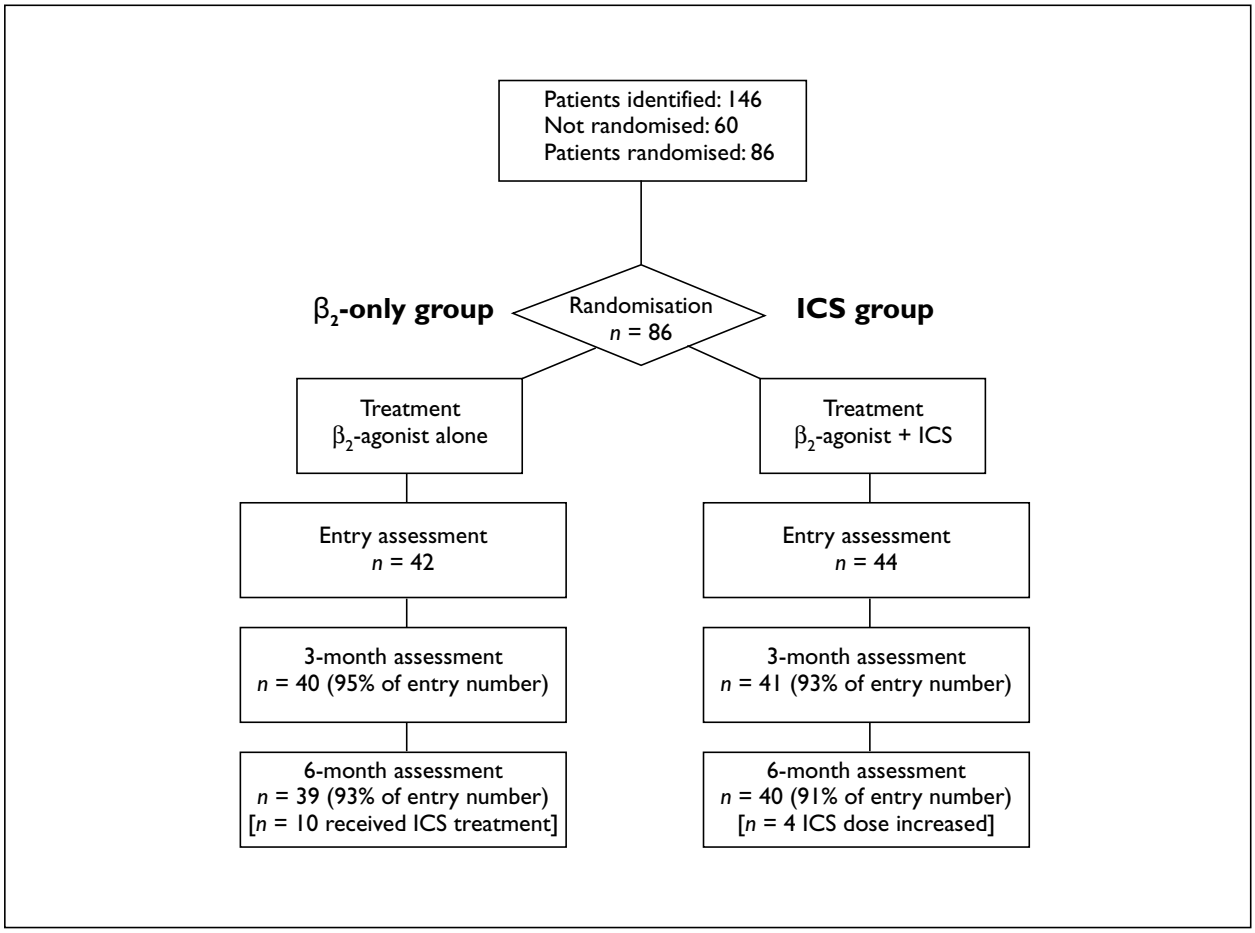

FIGURE 1 *Study design*

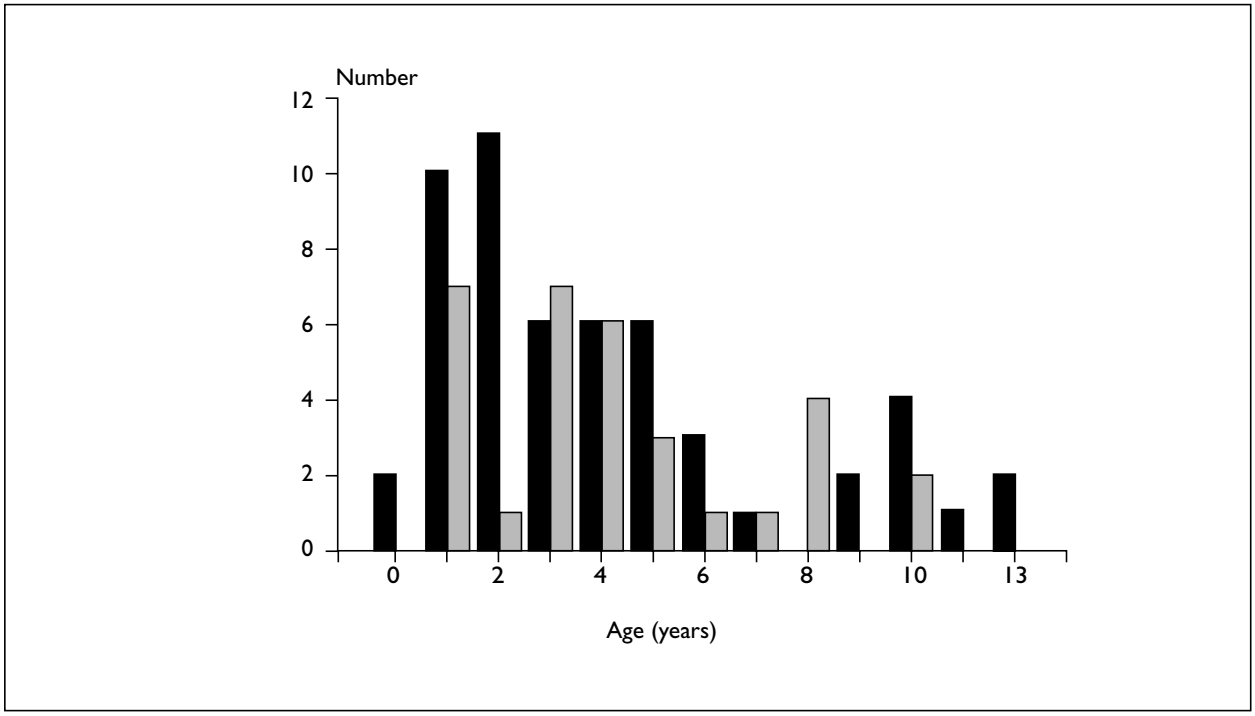

FIGURE 2 *Distribution of subjects by age group and gender (■, males; ▩, females) (n = 86)*

TABLE 2 *Biographical details by treatment group*

	ICS (*n* = 44)	β_2-only (*n* = 42)
Age (years)*	4.5 (3.2)	4.9 (3.1)
Male: female	1.6:1.0	1.8:1.0
Birth weight (kg)*	3.20 (0.7)	3.39 (0.6)
Premature (< 36 weeks gestation) (%)	11.4	7.1
Birth order†	2 (1, 3)	1 (1, 4)

**Values mean (SD)*
† Values median (interquartile range)

TABLE 3 *Family history by treatment group*

	ICS (*n* = 44)	β_2-only (*n* = 42)
Parent atopic (%)	59	74
Mother atopic (%)	48	50
Father atopic (%)	30	38
Both parents atopic (%)	18	14
Sibling asthmatic (%)	41	38
Number of household members*	4 (2, 6)	4 (2, 6)
Household with at least 1 smoker (%)	48	24†
Household with a least 1 furry pet (%)	52	36

Atopy defined as at least one of the following diagnosed: asthma, hay fever or eczema
** Values median (interquartile range)*
† p < 0.05

Biographical and family history details

Subjects' biographical details are shown in *Table 2*. The mean age of the group was 4.7 (SD 3.1) years, with a sex ratio of approximately 2:1 in favour of males. No statistically significant differences were found between treatments in either birth weight (mean 3.3 kg; SD 0.6 kg), birth order (median 2; range 1–4) or percentage born premature (9%).

At least one parent with a history of atopy was seen for 67% of the entire sample; 49% of these had an atopic mother, 34.5% an atopic father, and in 16.5% of cases both parents were atopic. No significant differences were found between treatment groups (*Table 3*). In addition, 40% of the children had a sibling who also carried a doctor diagnosis of asthma, and 45% of homes had at least one furry pet. In 36% of cases, children lived within a household where at least one member was a smoker. It was found that significantly more of the ICS group homes contained a smoker (48% versus 24%, $p < 0.05$). The average number of household members was four (ranging from two to six).

Anthropometry

The physical characteristics of the subjects are shown in *Table 4*. On entry, there were no statistically significant differences between the groups in weight, height or length. However, the β_2-only group had significantly greater

TABLE 4 *Physical characteristics on entry and percent change from entry at 3 and 6 months by treatment group*

	Study entry (absolute values)		3 months (% change from entry)		6 months (% change from entry)	
	ICS	β_2-only	ICS	β_2-only	ICS	β_2-only
Weight (kg)	18.5 (1.3) (*n* = 44)	20.4 (1.4) (*n* = 42)	3.2 (0.5)† (*n* = 41)	4.3 (0.6)† (*n* = 40)	7.3 (0.6)† (*n* = 40)	9.2 (0.9)† (*n* = 39)
Height (cm)	105.8 (3.2) (*n* = 40)	109.2 (3.1) (*n* = 39)	1.9 (0.2)† (*n* = 37)	1.9 (0.2)† (*n* = 37)	3.7 (0.3)† (*n* = 36)	3.9 (0.5)† (*n* = 35)
Length (cm)	77.7 (1.3) (*n* = 5)	77.1 (3.4) (*n* = 4)	3.8 (0.4)† (*n* = 4)	4.5 (1.7) (*n* = 3)	7.9 (0.4)† (*n* = 3)	8.5 (2.2)† (*n* = 3)
Knee–heel length (mm)	252.7 (7.3) (*n* = 29)	274.0 (7.2)* (*n* = 28)	5.1 (1.6)† (*n* = 27)	2.4 (0.5)† (*n* = 28)	6.7 (0.8)† (*n* = 26)	5.1 (0.8)† (*n* = 25)

Values mean (SE)
** Between treatments, p < 0.05*
† t, change from study entry, p < 0.05

knee–heel length ($p < 0.05$). A secondary analysis (ANCOVA) controlling for the effect of age ($p < 0.001$) found that knee–heel length was not significantly different between treatment groups on entry. There were no significant differences between the groups in any variables at 3 and 6 months, although, as expected, all values significantly increased over time ($p < 0.05$).

The velocity of growth in stature over the 6 months was 0.13 (SE 0.01) compared to 0.15 (SE 0.01) cm/week for the ICS and β_2-only groups, respectively ($p > 0.05$). There was also no significant difference in knee–heel length velocity at either 4 weeks, 3 or 6 months ($p > 0.05$). At 4 weeks, the velocities were 0.75 (SE 0.34) compared to 0.80 (0.27) mm/week, and at 6 months, they were 0.59 (SE 0.06) versus 0.48 (0.06) mm/week for ICS and β_2-only, respectively.

In order to take into account the longitudinal nature of the knee–heel length measurements, a random-effects modelling procedure was utilised, and these results are summarised in *Table 5*. In order to improve accuracy of calculation, age was referenced to the mean age (3 years).

The random variables (*Table 5*) show the covariance matrix (correlations) for the model of knee–heel length with age. The within-individual variation for knee–heel length at level 1 of the model (33.60) was greater than its associated SE of the estimate (2.66), indicating that knee–heel length (as expected) increased significantly with time. Also shown is the covariance matrix for level 2; the intercept (constant/constant 199.27 ± 41.78), the covariance correlations between the slope and the intercept (constant/age 37.83 ± 15.83), and the slope (age/age 9.55 ± 13.60). The positive correlation between intercepts indicates that there were differences between individuals, and the positive correlation between slope and intercept indicates that the greater the knee–heel length the greater the increase with age. After each explanatory variable was adjusted for covariables and for other explanatory variables (*Table 5*), it can be seen that age and birth weight had significant effects on knee–heel length gain, inasmuch as the slope coefficients for these variables were greater than their respective SE of the estimate. No gender effect was found, which was indicated by the sex-effect slope coefficient being less than twice its associated SE of the estimate. No significant independent effect of treatment on knee–heel growth was found either.

Sexual maturation

All of the girls were pre-menarcheal. Six girls had some signs of pubertal development (four in the ICS group and two in the β_2-only group);

TABLE 5 *Multilevel regression analysis of knee–heel length (mm) growth adjusted for age, birth weight and treatment group*

Random variable	**Constant**	**Age**
	Level 1 (within individuals)	
Constant	33.60 ± 2.66	
	Level 2 (between individuals)	
Constant	199.27 ± 41.78	
Age	37.83 ± 15.83	9.55 ± 13.60
Explanatory variables	**Estimate**	**± SE of the estimate**
Constant	239.86	± 9.91
Age	30.28	± 1.16*
Birth weight	8.91	± 2.80*
Sex	–2.02	± 3.64
Treatment	–0.96	± 3.52

Values are means and SE of the estimate
For statistical accuracy, age is measured about an origin of 3 years
Sex coded as 0 = males, 1 = females
Treatment coded as 0 = β_2-only, 1 = ICS
**Significant independent effects*

80% of these were at breast stage 1 on entry, the remainder were at stage 2. At 6 months, 25% were at stage 1, 50% at stage 2 and 25% at stage 3. No statistically significant differences were found between the groups either on entry or at 6 months.

Seven boys had signs of pubertal development (three in the ICS group and four in the β_2-only group); 86% were at genitalia stage 1 on entry, the remainder at stage 2. At 6 months, 57% were at stage 1, 29% at stage 2 and 14% at stage 3. No statistically significant differences were found between the groups either on entry or at 6 months.

Pulmonary function

At study entry, 39 (45%) of the sample were able to perform spirometry manoeuvres. At entry, FVC and FEV_1 predicted for the ICS group were 91.4% (SE 6.9) and 120.4% (SE 6.9), respectively, compared to 93.9% (SE 4.5) and 121.1% (SE 4.5) that were predicted for the β_2-only group, with no statistically significant differences between the two treatment groups. No significant differences were found, in absolute values, between the groups for FVC, FEV_1, PEFR or flow rate at 50% FVC on entry, or at follow-up at 3 and 6 months (*Table 6*). However, the FEV_1 and PEFR of the control group had significantly increased at 6 months from baseline.

FRC and LCI could only be measured successfully in four subjects and only at study entry, as this procedure proved to be technically difficult and time consuming (*Table 6*). Tidal breathing parameters measured as t_{PTEF} related to t_E showed no difference between groups on entry (*Table 6*). At 6 months, t_{PTEF}:t_E had significantly increased in the β_2-only group ($p < 0.05$) but not in the ICS group, and there was a significant difference between groups at 6 months ($p < 0.05$). A secondary analysis controlling for age found that age was not a significant covariate ($p > 0.05$) for t_{PTEF}:t_E.

Bone mass

Due to the age-specific nature of the equipment available, bone mass could only be measured in children over 6 years of age. Bone density measures were therefore available on 27 subjects (*Table 7*), with no significant differences for BUA or VOS between the groups on entry

TABLE 6 *Lung function on entry and percentage change from entry at 3 and 6 months by treatment group*

	Study entry (absolute values)		3 months (% change from entry)		6 months (% change from entry)	
	ICS	**β_2-only**	**ICS**	**β_2-only**	**ICS**	**β_2-only**
FVC (l)	1.60 (0.2) (*n* = 19)	1.70 (0.2) (*n* = 20)	7.9 (4.6) (*n* = 16)	7.3 (5.5) (*n* = 18)	8.7 (4.5) (*n* = 17)	12.7 (6.3) (*n* = 17)
FEV_1 (l)	1.42 (0.2) (*n* = 18)	1.43 (0.1) (*n* = 20)	3.3 (4.0) (*n* = 16)	3.6 (3.9) (*n* = 15)	7.6 (5.7) (*n* = 16)	17.4 (7.6)† (*n* = 17)
PEFR (l/second)	1.71 (1.5) (*n* = 21)	1.66 (1.7) (*n* = 1.7)	13.4 (5.2)† (*n* = 19)	7.1 (12.4) (*n* = 20)	15.8 (6.7) (*n* = 20)	23.8 (7.7)† (*n* = 19)
Flow rate at 50% FVC (l/second)	1.95 (0.2) (*n* = 17)	2.1 (0.2) (*n* = 15)	6.2 (8.8) (*n* = 14)	–6.9 (8.86) (*n* = 15)	17.4 (9.1) (*n* = 16)	9.5 (8.7) (*n* = 15)
Infant lung function						
t_{PTEF}:t_E (%)	30.1 (1.2) (*n* = 30)	29.5 (1.7) (*n* = 25)	2.8 (6.1) (*n* = 26)	8.9 (6.6) (*n* = 25)	–3.9 (5.4) (*n* = 26)	21.8 (9.6)*† (*n* = 22)
FRC (l)	0.31 (*n* = 2)	0.63 (*n* = 2)	–	–	–	–
LCI	12.7 (*n* = 2)	8.0 (*n* = 2)	–	–	–	–

Values mean (SE)

**Between treatments, p < 0.05*

†t, change from study entry, p < 0.05

TABLE 7 *Bone mass and bone metabolism on entry and percentage change from entry at 3 and 6 months by treatment group*

	Study entry (absolute values)		3 months (% change from entry)		6 months (% change from entry)	
	ICS	**β_2-only**	**ICS**	**β_2-only**	**ICS**	**β_2-only**
BUA	53.0 (4.7) (*n* = 13)	55.5 (5.0) (*n* = 15)	–2.1 (6.5) (*n* = 11)	14.8 (11.2) (*n* = 10)	–10.3 (5.7) (*n* = 11)	2.7 (11.4) (*n* = 12)
VOS	1702 (14.5) (*n* = 13)	1672 (9.0) (*n* = 15)	0.004 (0.7) (*n* = 11)	0.39 (0.4) (*n* = 10)	–1.3 (1.2) (*n* = 10)	0.17 (0.8) (*n* = 12)
Urinary pyridinoline:creatine	270.6 (16.3) (*n* = 39)	254.8 (22.3) (*n* = 33)	–4.1 (10.3) (*n* = 27)	13.2 (6.1) (*n* = 34)	–12.4 (5.1)† (*n* = 26)	25.2 (11.1)* (*n* = 29)
Urinary deoxypyridinoline: creatine	78.8 (5.5) (*n* = 39)	73.3 (6.1) (*n* = 33)	–1.2 (10.5) (*n* = 27)	14.3 (6.4) (*n* = 34)	–9.9 (5.2)† (*n* = 26)	27.2 (11.9)* (*n* = 29)

Urinary metabolites measured in evening spot sample

Values mean (SE)

* *Between treatments,* p < *0.05*

† *t, change from study entry,* p < *0.05*

or at subsequent follow-up. A secondary analysis adjusting BUA and VOS for age also found no difference between treatments.

Bone metabolism

Measures of urinary pyridinoline and deoxypyridinoline were normalised by relating them to urinary creatine. *Table 7* presents data collated from evening spot urine. No significant differences were found between the groups for entry levels of these metabolites. At 3- and 6-month follow-ups the ICS group showed a reduction in metabolites compared to the β_2-only group in whom an increase was seen, although this difference did not reach statistical significance until 6 months ($p < 0.05$).

A secondary analysis correcting for the significant effect of age ($p < 0.001$) confirmed the significant difference between treatments ($p < 0.05$).

Health status

On entry to the study, 46% of the ICS group and 45% of the β_2-only group had more than four episodes of wheeze in the preceding 12 months (*Table 8*). The incidence of wheeze decreased significantly in both groups over time ($p < 0.05$) and at 6 months the percentage with four or more episodes of wheeze during this period was 25% and 18%, respectively, for the ICS and β_2-only groups ($p > 0.05$). Sleep disturbance due to wheeze was noted as 25% in the ICS group at

TABLE 8 *Health status on entry and at 3 and 6 months by treatment group*

	Study entry		3 months		6 months	
	ICS (*n* = 44)	**β_2-only (*n* = 42)**	**ICS (*n* = 41)**	**β_2-only (*n* = 40)**	**ICS (*n* = 40)**	**β_2-only (*n* = 39)**
Episodes of wheeze > 4 (%)	45.5	45.2	26.8†	17.5†	25.0†	17.9†
Sleep disturbance due to wheeze > 1 per month (%)	25.0	36.6	24.4	22.5	10.0†	17.9
Dry cough at night (%)	86.4	83.3	44.2†	50.0†	39.5†	45.2†
Sleep disturbance due to cough > 1 night per week (%)	47.4	61.1	22.7	43.5	40.0	21.7
Wheezing limits child's speech (%)	20.5	16.7	11.6	16.7	7.0	9.5

† *Z statistic, change from study entry,* p < *0.05*

entry, and this showed a significant reduction to 10% ($p < 0.05$) at 6 months. The incidence of sleep disturbance in the β_2-only group was 37% on entry, with a non-significant reduction to 18% at 6 months. Group comparisons showed no significant difference in occurrence of sleep disturbance due to wheeze at either entry or follow-up. Night-time cough was observed in 86% of the ICS group compared to 83% of the β_2-only group, and this reduced significantly in both groups to 40% and 45%, respectively ($p < 0.05$), but with no significant differences between treatments. Wheezing limited the speech of 21% of the ICS group and 17% of the β_2-only group, with no significant difference between treatment groups, although, unlike other symptoms, speech limitation did not change significantly over time.

Self-report asthma diary

No statistically significant differences were found between treatment groups after 3 and 6 months with regard to number of symptom-free days, symptom score or number of times 'rescue' treatments with β_2-agonist were required (*Table 9*). However, in the β_2-only group, the number of symptom-free days significantly increased during the 3-month period ($p < 0.05$), and average night-time symptom score and use of reliever during the day significantly decreased ($p < 0.05$). At 3-month follow-up, 58% of the ICS group had fewer symptom days, 8% had no change and 34% had more symptom days, compared to 56%, 13% and 31%, respectively, in the β_2-only group. All were non-significant between groups. In addition, no significant differences were found either between groups or within groups over time with regard to number of days of school/nursery missed due to asthma or number of visits to a GP or hospital.

QoL

PACQLQ

There was no significant difference with regard to caregivers' QoL between treatment groups on entry into the study (*Table 10*); baseline CGTot, CGEmot and CGAct were 5.2, 5.4 and 5.0, and 5.4, 5.6 and 5.3 for the ICS and β_2-only groups, respectively (1 = worst, 7 = best). In both groups, QoL (CGTot, CGAct and CGEmot) had significantly improved by 6 months ($p < 0.05$), but the improvement was the same in both treatment groups and no significant treatment effect was observed. *Table 11* shows Pearson *r* correlations between changes in PACQLQ scores (*Table 10*) and changes in symptom (*Table 11*) over the final 3 months of the study. All correlations were significant, but moderate. Changes in symptoms explained between one-quarter and one-third of the observed variance (r^2) in PACQLQ. Changes in both day and night reliever usage (*Table 11*) were also significantly associated with changes in CGTot, CGAct and CGEmot.

A subanalysis of Pearson *r* correlations of children aged 7 years and younger again showed significant but moderate correlations (ranging

TABLE 9 *Thirty-one-day asthma diary recorded prior to visits at 3 and 6 months by treatment group*

	3 months		6 months	
	ICS (*n* = 39)	**β_2-only (*n* = 33)**	**ICS (*n* = 36)**	**β_2-only (*n* = 33)**
Number symptom-free days in 31 days	23 (14, 28)	24† (16, 30)	28 (16, 31)	27 (20, 30)
Total night-time symptom score*	6 (0, 20)	3† (0, 14.5)	2 (0, 13)	2 (0, 6)
Total daytime symptom score*	10 (2, 22)	5 (0, 19)	3 (0, 24.5)	3 (0, 12)
Total times night-time reliever used	0 (0, 10)	1 (0, 8.5)	0 (0, 5)	0 (0, 4)
Total times daytime reliever used	6 (0, 17)	4† (0, 26)	0 (0, 13.5)	3 (0, 10)
Total number days of school/nursery missed	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Total number of visits to GP	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Total number of visits to hospital	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Values median (interquartile range)				

* *Symptoms were scored from 0 (none) to 5 (most severe) and summed over diary days, giving a maximum score of 155*
† *Z statistic, change from study entry,* $p < 0.05$

TABLE 10 *Caregivers's QoL on entry and at 3 and 6 months by treatment group*

PACQLQ	Study entry		3 months		6 months	
	ICS (*n* = 43)	β_2-only (*n* = 42)	ICS (*n* = 41)	β_2-only (*n* = 40)	ICS (*n* = 40)	β_2-only (*n* = 39)
CGTot	5.2 (4.4, 5.8)	5.4 (4.7, 6.2)	6.1 (5.4, 6.5)	5.9 (5.2, 6.8)	6.2* (5.7, 6.8)	6.4* (5.3, 6.8)
CGEmot	5.4 (4.2, 6.1)	5.6 (5.0, 6.1)	6.1 (5.4, 6.6)	6.0 (5.1, 6.7)	6.2* (5.6, 6.8)	6.6* (5.6, 6.8)
CGAct	5.0 (4.0, 5.5)	5.3 (4.3, 6.0)	6.0 (5.3, 6.5)	6.0 (5.5, 7.0)	6.5* (5.3, 7.0)	6.3* (5.5, 7.0)

All PACQLQ total (CGTot) and subscale (CGEmot, CGAct) scores range from 1 (worst) to 7 (best)

Values median (interquartile range)

Z, change from study entry, p < 0.05

TABLE 11 *Changes in caregivers's QoL and changes in symptom frequency (over diary days) at 3 and 6 months for all patients*

Changes in symptoms and reliever use (month 3 to month 6)	Changes in cargiver's QoL (month 3 to month 6)		
	CGTot	CGAct	CGEmot
Symptom-free days	0.51*	0.47*	0.52*
Day symptom score	–0.54*	–0.52*	–0.52*
Night symptom score	–0.54*	–0.52*	–0.50*
Daytime reliever use	–0.46*	–0.44*	–0.44*
Night-time reliever use	–0.29*	–0.32*	–0.24*

Values Pearson r correlation

p < 0.05

from 0.50 to 0.56) between changes in PACQLQ scores and changes in symptoms ($p < 0.05$). Juniper and colleagues[101] have defined a change of 0.5 or more in children's PACQLQ scores as clinically significant. Although change in parent scores was correlated with change in PACQLQ scores, less than half (29; 44%) of the parents showed 0.5 or higher absolute changes in their PACQLQ scores during the study. We defined the 33 parents who showed a < 0.5 change in PACQLQ scores as 'low responders'.

Table 12 shows that low responders did not differ from 'responder' parents in child symptom-free days on entry to the study (19.1 versus 19.5, $p > 0.05$) or change in symptom-free days over the period of the study (average number of days improvement: 2.8 versus 2.3, $p > 0.05$), but they had higher PACQLQ scores on entry to the study (6.0 versus 5.2, $p < 0.01$). Over the 3 months, responder parents showed a mean change of 1.4 in PACQLQ score, compared to 0.2 for low-responder parents. Low responders did not differ in social characteristics to responder parents, such as mother's age ($p > 0.05$), smoking in the household ($p > 0.05$) or deprivation category ($p > 0.05$), or in birth order of study child ($p > 0.05$) or initial birth weight ($p > 0.05$).

CAQs

Fifty per cent of the children ($n = 43$) were too young to be able to complete the questionnaires (mean age 2.3, range 0.4 to 4.2 years). At study entry, 27 children completed CAQA (mean age 5.2, range 3.6 to 7.4 years), 12 completed CAQB (mean age 9.9, range 8.4 to 11.1 years) and two completed CAQC (mean age 13.4, range 13.1 to 13.8 years).

The only significant findings with regard to children's QoL measurements (*Table 13*) were that in the youngest age group (CAQA) the β_2-only group had a significantly higher quality of living score and higher distress score ($p < 0.05$) at 6 months than the ICS group, although these were not significantly higher than the scores on entry (*Table 13*). Changes in CAQ measures did not correlate with either symptoms or reliever usage changes ($p > 0.05$).

TABLE 12 *Symptoms and QoL by responder type in children less than 7 years of age*

	Low responder *n* = 33	Responder *n* = 26	*p*
Mean initial symptom-free days (SD)	19.1 (1.7)	19.5 (2.1)	0.9*
Mean initial total PACQLQ (SD)	6.0 (0.18)	5.2 (0.18)	0.01*
Mean change in symptom-free days (SD)	2.3 (9.4)	2.8 (11.4)	0.86*
No. children with worsening of ≥ 5 symptomatic days (%)	5 (14.7)	4 (14.3)	0.97†
No. children with improvement of ≥ 5 symptom-free days (%)	9 (30.0)	10 (40.0)	0.44†
Mean maternal age (SD)	30.1 (5.0)	28.6 (4.9)	0.31
Median deprivation category	2.0	3.0	0.90†
Mean age of child (SD)	3.8 (1.5)	3.2 (1.7)	0.24*
Birth order (%)	19 (58)	11 (42)	0.24†
Birth weight, kg (SD)	3.3 (0.71)	3.4 (0.67)	0.68*

* *Independent samples* t *test*
† *Chi-squared test*

TABLE 13 *Child QoL on entry and at 3 and 6 months by treatment group and age-appropriate questionnaire*

	Study entry		3 months		6 months	
CAQs	**ICS**	**β_2-only**	**ICS**	**β_2-only**	**ICS**	**β_2-only**
CAQA	*n* = 15	*n* = 12	*n* = 15	*n* = 12	*n* = 15	*n* = 12
Quality of living score	34 (32, 36)	32 (30, 36)	31 (31, 34)	34 (29, 38)	33 (25, 33)	35* (33, 37)
Distress score	8 (4, 12)	6 (4, 9)	6 (4, 10)	5 (4,9)	7 (6, 10)	4* (2, 6)
CAQB	*n* = 8	*n* = 5	*n* = 8	*n* = 5	*n* = 8	*n* = 5
Active quality of living score	28 (24, 31)	29 (27, 30)	28 (23, 34)	29 (24, 32)	31 (27, 34)	28 (25, 29)
Passive quality of living score	17 (13, 19)	18 (16, 19)	17 (15, 19)	18 (16, 20)	17 (16, 19)	16 (15, 18)
Distress score	21 (19, 24)	24 (21, 25)	23 (16, 25)	24 (23, 24)	22 (19, 22)	23 (18, 25)
Severity score	10 (8, 14)	13 (11, 16)	9 (6, 12)	10 (7, 14)	10 (6, 12)	9 (6, 12)
CAQC	*n* = 0	*n* = 2	*n* = 0	*n* = 2	*n* = 0	*n* = 2
Active quality of living score	–	33	–	30	–	39
Teenage quality of living score	–	22	–	23	–	23
Distress score	–	44	–	44	–	44
Severity score	–	16	–	19	–	17
Reactivity score	–	20	–	21	–	20

See Box 2 *for scoring systems*
Values median (interquartile range)
* χ^2 *between treatments,* $p < 0.05$

Economics

There were no outpatient visits or inpatient stays recorded in either arm in the 6 months following entry to the trial. However, the pilot data did enable a comparison to be made between the arms with respect to prescribing costs and GP consultations. As it can be seen in *Table 14,* the mean prescription cost was significantly higher for the patients assigned to the early prophylaxis arm. The prescription costs of patients in the prophylaxis arm were £20.73 higher over the 6-month period (95% CI, £12.18 to £29.28). There was no significant difference between the two arms for the mean cost of both asthma- and non-asthma-related GP consultations. The cost of the three categories of healthcare combined was significantly higher for patients assigned to the ICS arm, averaging £16.97 more than the control group over 6 months (95% CI, £3.21 to £30.73).

TABLE 14 *Cost of prescriptions and GP consultations*

	β_2-only *n* = 42	ICS *n* = 37	Probability (2-tailed test)
Prescription costs	16.06 (339.7)	36.79 (390.0)	< 0.001
Non-asthma GP consultations	14.50 (351.6)	12.57 (245.9)	0.619
Asthma-related GP consultations	15.86 (184.1)	14.03 (194.5)	0.557
Total	46.42 (1073.0)	63.39 (788.6)	0.015
Values mean (total variance) in £s			

TABLE 15 *Incremental cost per change in t_{PTEF}:t_E and proportion of symptom-free days*

	β_2-only *n* = 42	ICS *n* = 37	Probability (2-tailed test)
Change in t_{PTEF}:t_E at 6 months	0.0119 (0.123) *n* = 17	0.0049 (0.008) *n* = 22	0.832
Proportion of symptom-free days in the third month	0.648 (0.109) *n* = 35	0.646 (0.115) *n* = 38	0.988
Proportion of symptom-free days in the sixth month	0.766 (0.095) *n* = 32	0.708 (0.093) *n* = 35	0.441
Not all individuals had both economic and functional/symptomatic assessments			
Values mean (total variance) in £s			

There were no significant differences between the two arms in terms of any of the effectiveness measures. There were too few observations for absenteeism from school for a comparison to be made. *Table 15* presents the results for the change in t_{PTEF}:t_E over the 6 months and for the proportion of symptom-free days in the third and sixth months.

Chapter 4
Discussion

Despite a greater awareness of the disease and improved treatment, asthma remains the most common chronic disease of childhood. Although in the future modification of the child's early environment may reduce the disease prevalence,[61] the best available approach currently is early identification and initiation of therapy. Our recruitment results confirm reports from outside the UK[22,23] that the majority of wheezing/asthmatic children are being managed with long-term ICS. The proportion of the symptomatic population on ICS is likely to increase further as more GPs implement the revised BGAM.[25] However, differences between various national and international guidelines indicate a need for evidence-based approaches founded on both explanatory and pragmatic trials, similar to the one presented.[102]

Study design

The pilot trial had features of both explanatory and pragmatic designs. Typically, explanatory trials address the question 'can the intervention in a near ideal setting (that is in a tightly controlled and defined environment) have a particular effect'. Pragmatic trials compare policies of management used in normal practice in terms of patient outcome and resources used. Our design was explanatory in the sense that we used a number of surrogate measures of outcome (such as pulmonary function tests and measure of bone turnover) over a relatively short timescale. Pragmatic features were the clinically based eligibility criteria, the open (as opposed to placebo-controlled) design, the use of patient assessed measures of outcome, and the consideration of resource use. The advantage of the surrogate markers is that they are likely to be more sensitive to treatment differences; their disadvantage is their uncertain relationship with substantive measures of final outcome and hence relevance to the health services. Arguably, the most controversial aspect of our design was the open allocation to either ICS or symptomatic treatment only. The basis of this design was that we thought this would reflect the ways that ICS would likely be used in actual general practice, and that this design would be more acceptable and attractive to both the GPs and the parents and children. It also enabled an assessment of the differential impact that these policies might have on the NHS, including resource use. The disadvantages were that 19% of children in the β_2-only group were subsequently treated with ICS in the 6-month period. Although this does not introduce bias into the comparison of the two policies, it clearly blunts the comparison of short-term outcome. Obviously, the larger the number of such 'crossovers', the bigger the problem this would become in a pragmatic design. Up to a 10% crossover rate is usually considered acceptable, but rates above this level would have an important impact on statistical power. If the trial had been performed on a larger scale, this issue of adherence to allocation is one to which we would have put greater emphasis. Having acknowledged this issue, however, we are not in a position to know how many participants in a placebo-controlled trial would have (later) been prescribed ICS, and there are therefore arguments for both higher and smaller proportions. Furthermore, the use of a placebo in such situations complicates normal practice, because the clinician needs to unblind before deciding on future management. We are also uncertain whether as many parents with their children, and indeed GPs, would have agreed to participate in such a placebo-controlled trial. As we wished to investigate the effect of ICS as a generic class, we would have required placebo products for all manufacturers and delivery devices. This would clearly be impractical unless a single company's product was used, and we consider that one of the strengths of our study was the fact that it was not linked to a single company. There has been surprisingly little formal research evaluating the potential advantages and disadvantages of open as opposed to placebo-controlled trials with respect to recruitment rates, adherence to treatment, in balancing other co-interventions, and biased assessment of outcome. Given its interests in assessing the impact of new technologies on the NHS, this is a methodological issue that the NHS Research and Development HTA programme may wish to address in methodological research.

As previously discussed, although the treatment could have been blinded, we suggest that a pragmatic randomised study without placebo

control for the early introduction of ICS would still enable a definitive result to be obtained. We would, however, suggest that the design be improved by blinding the assessor. Future studies might consider ensuring that the individual recruiting the subjects and the individual assessing the response be separate, and that the assessor should not be aware of the guideline step on which the subject was placed. In the current study, the same individuals were responsible for both recruiting and assessments.

A definitive study with increased numbers might address the issue of dosage titration and thus control for possible confounders associated with delivery device, type of ICS and associated variability of absorbed doses. However, such a study design would have to ensure balance not only on age, sex and general practice, as in the present study, but also on type of ICS, dosage and delivery device. In practice, such a study design is unlikely to be feasible.

Asthma prevalence

Given the limitations of the present study, we believe that this trial has produced some interesting results and raised a number of answerable questions. Our initial audit of the general practices involved confirmed the high population prevalence of both childhood wheezing and diagnosed asthma, and, although not as high as the 20% reported in the 1994 Aberdeen school survey,[5] the 11% found in the present sample is similar to the 14% found in a young adolescent population in the Highlands.[6] Although not an unsurprising finding in itself, the fact that two-thirds of these children were already being treated with an ICS further suggests the need to monitor the long-term risks, costs and benefits of their early introduction, particularly in the pre-school child, and the fact that one-third of parents declined the opportunity of being involved due to concerns with regard to steroid safety emphasises this.

Recruitment

Despite the large percentage of symptomatic children using regular ICS, 96% of the target 90 children were recruited. The fact that the age distribution was skewed towards the lower age range highlighted the young age of the majority of newly presenting wheezing children. The small numbers recruited in the older age groups suggests that by these ages children are unlikely to be naïve to ICS therapy. Whilst the results suggest that the study design could be translated into a definitive trial in pre-school children, in order to ensure adequate numbers in older children a multicentre design might have to be utilised.

The clustering of recruitment in the pre-school child is a potential weakness of the study in that a number of these pre-school children may not have classical atopic asthma but rather transient virally induced wheeze.[7] The fact that airway obstruction in children results from a number of different pathophysiological processes could also have confounded our results.[7] If early intervention with anti-inflammatory treatment is to be studied effectively, it would be necessary to differentiate the 'true' asthmatics at risk from chronic airway inflammation and remodelling from those with transient virally induced wheeze.[7,8] Studies of the natural history of the disease have shown that a relatively low percentage of pre-school children with wheeze continue to wheeze in their early school years.[10,12,16] Although these studies suggest that childhood asthma is a heterogeneous condition, a number of other studies have found a strong association between atopy and the persistence of wheeze.[12,17,91,103] This association also appears to operate from early childhood. A Finnish study investigating the 1-year outcome of children hospitalised for wheezing found that a family history of atopy was associated with an increased risk of subsequent asthma.[104] The short time period of the present pilot study does not allow any inferences to be drawn with regard to the natural history of the disease, however, the fact that over two-thirds of the subjects had a family history of atopic disease suggests that further investigation and follow-up of these individuals is warranted.

It is also possible that the present study's recruitment strategy of identifying patients retrospectively resulted in a bias in favour of recruitment of milder asthmatics, i.e. the severity of the disease has not yet warranted ICS therapy. It is possible that a more severe group would have shown deterioration over the short term and thus may have been more responsive to the treatment. Although, we attempted to control for this bias by recruiting subjects whose symptoms had commenced in the previous 12 months, we would propose that a future study might consider only recruiting subjects prospectively.

Whilst recognising the fact that asthma in childhood is comprised of more than one clinical

syndrome and that the optimal approach to treatment may differ between these different syndromes, we believe that we should not exclude the pre-school child from future studies. Rather than excluding this age group, we would emphasise that as this is the largest group presenting in primary care, future studies should concentrate on this young age group. It may, therefore, be more appropriate that wheeze rather than asthma is used as an entry criterion in a future study of symptomatic pre-school children. Arguably, it is the pre-school child where most concerns have been expressed with regard to steroid safety, and thus they are the group where long-term use of ICS should be studied more closely.

Other environmental factors may also have to be taken into account when identifying appropriate children for recruitment to a definitive study. Established risk factors for adult onset of wheeze include low socio-economic status and parental smoking,[103,104] and although the results from the present study lend some weight to the latter in that nearly half of the families reported having at least one smoker in the household, the majority of children came from families in the higher socio-economic groups, which is a likely reflection of our choice of general practices.

Acceptability of protocols

One of the objectives of this pilot study was to establish the acceptability of the protocols used, namely whether or not a child/parent completed the assessments. We now recognise that this area of investigation might have been improved by conducting interviews with the families to discuss their feelings about participating in the study, and whether they would be willing to participate in a longer-term study.

Although 8% of the sample withdrew from the study, none cited the protocol as a reason, but rather family time constraints and leaving the region. At study entry, all subjects completed the health status and family history questionnaire. The caregiver's QoL questionnaire was also completed by all parents, but only 50% of the children were able to complete the child-centred QoL questionnaire. Eighty eight percent of the parents completed an asthma symptom diary. All children had complete age-appropriate anthropometry and were able to perform at least one of the pulmonary function assessments. We found that measures of bone mass could only be measured in children over 6 years of age due to the age-specific nature of the equipment. In those children able to be measured ($n = 29$), a value was obtained in 90% of cases. We also found that 97% of children provided a urine sample for assessment of bone metabolism, and with regard to the economic assessment we were able to assess this in 92% of the sample.

We believe the low drop-out rate and high compliance with the measurements indicates that the protocols presented in this report would be acceptable and feasible if used in a long-term study. The usefulness of the individual outcomes used is discussed in more detail later.

QoL

We piloted two QoL assessments. One assessed the impact of the disease on family life, the PACQLQ,[54] and the other was a child-centred assessment, the CAQ.[49] To be useful as an outcome measure in clinical interventions in asthma, QoL evaluations must be sensitive to change in fundamental aspects of asthma. We sought to assess the performance of these two instruments in the setting of a clinical asthma trial, and to address the relationship (if any) between symptom reporting and perceived parental and child-centred QoL.

PACQLQ

With regard to the PACQLQ, we sought to assess if change in a child's symptoms was associated with a change in a caregiver's QoL (CGQoL). Juniper and colleagues[54] carried out an original validation of this questionnaire in parents of children aged 7 to 17 years, and we are not aware of any other study that has assessed the PACQLQ for parents of the pre-school age group. As already discussed, the present sample of children probably represents the milder end of the wheezing illness continuum. Over the final 3 months of the study, symptom frequency was assessed by symptom diary and was found to decrease in both groups. Although initial PACQLQ scores were high (indicating good QoL), the change in total PACQLQ score (CGTot) was significantly related to changes in the symptoms of the child over 3 months. The PACQLQ appears to be sensitive to impairment in family functioning, and the emotional well being of parents of pre-school children, even when child symptoms are relatively mild.

Although correlation between change in symptoms and change in CGQoL was significant, closer analysis showed that parents differed in their CGQoL scores with symptom changes. Juniper and co-workers[101] have suggested that a minimum score change of 0.5 is necessary to reflect a clinically significant change in a child's QoL. When we used this criterion to identify parents who did or did not show clinically significant change in QoL, we found that although most parents altered in PACQLQ scores as symptoms changed, some parents showed smaller absolute change in PACQLQ (i.e. less than 0.5). It appeared that parents differed as to how burden of care, as measured by PACQLQ, altered as symptoms changed in their child. The observed change in child symptoms, and direction of change were similar in low-responder and responder groups, however, the low responder groups were significantly higher (better) in their initial PACQLQ. It seemed that from the beginning of the study, some parents were more resilient to child symptoms, and less affected by change in symptoms.

Although our results suggest that the PACQLQ cannot predict individual parental response to symptom change in their child, they do support the validity of the PACQLQ as an outcome measure for clinical interventions. We would therefore recommend its use in future asthma trials in the pre-school age group.

CAQs

French and co-workers[49] have developed three CAQs, which are child-centred and disease-specific, for children aged 4 to 16 years. The questionnaires utilise a five-point 'Smiley' scale, which is represented by five faces, ranging from very happy to very sad. The scale assesses children's attitudes towards different aspects of school/pre-school life. The advantage of using three questionnaires is that they allow for the fact that patterns of daily activity and cognitive abilities of children differ as they develop. The major disadvantage of the questionnaires is that they are not interchangeable because they all measure different QoL parameters, and, for use in longitudinal studies, the same questionnaire would need to be used at each measurement occasion. The age range of the present study sample precluded its use in over half the children and only two subjects completed CAQC. Our results from the CAQAs and CAQBs, albeit in a small sample size, indicated that the questionnaires were not sensitive to changes in symptoms or reliever usage. The results from this pilot study, therefore, suggest that the CAQ is, perhaps, not a sensitive enough measure of QoL in the pre-school child.

Short-term outcomes associated with ICS treatment

The use of anti-inflammatory pharmacotherapy (particularly ICS) is now the cornerstone of childhood asthma management.[21,25] ICS have been shown to confer significant protection against exacerbation of asthma leading to hospitalisation[21,22] and a significant reduction in requirement for oral steroids.[29] However, reports have started to appear that question their effectiveness in the treatment of wheeze in the pre-school child.[103]

Pulmonary function

Whilst previous studies in children have shown that adding ICS to inhaled β_2-agonist treatment improves lung function (assessed by spirometry),[20,105] this was not found in the present sample. This could be a possible consequence of the small number of children who were able to perform these age-dependant pulmonary tests, and the, perhaps, mild nature of the disease in this asthma population.

As the majority of children were below 6 years of age, tidal breathing pattern analysis was the predominant lung function outcome measured.[82] Tidal breathing was assessed using RIP. It was found that the $t_{PTEF}:t_E$ ratio significantly improved in the β_2-only group whilst remaining unchanged in the ICS group. This finding, albeit in a much younger age group, was the opposite of that seen in pulmonary function studies of older children.[20,105] Although the within-subject variability of $t_{PTEF}:t_E$ in infants has led some authors to question its suitability as a clinical and epidemiological tool,[78] van der Ent and colleagues,[82] in a population of similar age to our own, found that $t_{PTEF}:t_E$ measured by pneumotachography through a mouthpiece correlated significantly with forced maximal expiratory flow volume parameters, and was able to distinguish differences between patients with asthma and healthy age-matched controls. This group also found that $t_{PTEF}:t_E$ values significantly increased in asthma patients after administration of bronchodilator drugs.[82] Recent comparisons between the two assessment methods of $t_{PTEF}:t_E$ have shown that RIP can measure tidal breathing parameters as reliably as the pneumotachograph system in young pre-school children and is better tolerated.[106]

The present pilot study has shown that whilst the measurement of tidal breathing parameters by RIP is well tolerated by young children, the large within- and between-subject variability of the test (*Table 6*) suggests that it has limited use in its present form in the assessment of airways obstruction in this age group. We are currently developing new techniques using more appropriate analysis of the waveforms created by inductance bands. Our initial studies show the potential of this approach in identifying subclinical evidence of airflow obstruction and assessment of response to therapy.[107,108] However, as this new waveform analysis is still in the early stages of development, we suggest that other techniques, such as respiratory resistance,[109] might be used at present to measure airways obstruction in a definitive trial of pre-school children.

Growth

Although the positive benefits of ICS treatment are well established, increasing use of higher doses of ICS have heightened concern over their potential systemic effects, particularly with regard to possible growth retardation in children.[29,70] Evidence of significant side-effects of ICS is conflicting. Retrospective studies have suggested that when asthma control is accounted for, the effects of ICS on linear growth are minimal.[27] The present study confirms these findings with no effects being observed with regard to changes in velocity of growth (stature); results that conflict with other prospective studies that suggest that growth is significantly decreased during childhood.[32,33]

Short-term linear growth was assessed using knemometry,[36] a technique that is useful for showing acute effects of an intervention in infancy, but less useful in older children in whom it is a poor predictor of long-term growth.[36] The velocity of knee–heel length growth was not significantly affected by early introduction of ICS in the present study. A random-effects modelling procedure,[99] which allowed all individuals to have their own growth curves, also failed to find any significant difference between the two treatment groups. However, the results should be interpreted with caution due to the small sample size ($n = 41$). These results contradict those of another study of mildly asthmatic children of 6 to 13 years of age receiving 200–800 µg budesonide daily, in whom a dose-dependent reduction in lower leg growth was observed when measured by knemometry.[37] Similarly, low doses of inhaled BDP have also resulted in a marked reduction in short-term lower leg growth in two studies in steroid- and non-steroid-dependent childhood asthma.[37,38] The relevance of short-term lower leg length is uncertain as discussed above, but Doull and colleagues[32] have reported asthmatic children receiving low doses of ICS to be 0.8 cm shorter than a matched placebo group following 9 months of regular therapy. Tinkelman and co-workers[39] also noted that inhaled BDP caused growth velocity suppression when compared to theophylline in long-term treatment of asthmatic children.

As poorly controlled asthma is known to influence growth,[40] it is possible that the growth suppressive effect of ICS may be counterbalanced to some extent by the beneficial anti-inflammatory effects of the drug.[37] We suggest that a definitive trial should be long term, for at least 5 years, and that whilst knemometry is a useful surrogate for linear growth in the short term, its relationship to long-term growth is questionable and thus would preclude its use in a longer-term study.

Growth velocity, particularly during mid- to late childhood, is affected by the chronological age at which sexual maturation occurs. Although recent attention has focused on possible effects of ICS therapy on linear growth, the effects of asthma (or any chronic disease) on pubertal delay are well documented.[40] While it was first thought that persistent asthma could significantly reduce growth potential, longitudinal studies have confirmed that puberty is merely delayed and that target adult height is eventually achieved.[40] Due to the small numbers recruited in the pubertal age group in this study, it is not possible to add any further evidence to the discussion, other than to, perhaps, emphasise that in any growth assessments during the pubertal period it is essential to make some assessment of sexual maturity.

Bone metabolism

Pyridinoline and deoxypyridinoline are cross-linking amino acids of collagen that are located mainly in bone and cartilage. When bone matrix is resorbed these crosslinks are quantitatively excreted in the urine and thus represent specific markers. In studies of malnourished children, pyridinoline and deoxypyridinoline have shown that the turnover of the skeleton is greatly reduced in malnutrition and that it responds rapidly to nutritional intervention.[110] It is, therefore, not unreasonable to assume that pyridinoline and

deoxypyridinoline would increase as children grow. There was no significant difference in linear growth between the ICS and β_2-only groups; however, there was a significant difference in the levels of pyridinoline and deoxypyridinoline at the end of the study period. Values of pyridinoline and deoxypyridinoline significantly decreased from baseline in the group receiving ICS treatment whilst increasing in the control group.

These results suggest systemic effects of ICS, which in our case was not associated with any suppression of linear growth. These results are in accord with other studies in children, which have found that levels of bone formation and bone degradation decrease during ICS treatment while not affecting linear growth.[111] The results presented from this study are taken from evening spot urine samples, which was found to be the best collection technique. Although an overnight urine sample would be the preferred choice in older children, only 37% of children under 6 years of age in the present sample were able to attempt this assessment. In contrast, 80% of the same age group were able to provide an evening spot urine sample. Thus, when developing protocols for a definitive study, the age range of the children under study should be taken into account when deciding on the urine collection protocol to be used.

Bone mass

One possible interpretation of our data is that the systemic effect of ICS, in moderate dosage, may be on bone architecture and bone mineral density, rather than on linear growth. Although, adult studies have found an association between reduced bone mineral density and ICS therapy,[112,113] no adverse effects have been observed in children.[113] Bone mineral density was not measured in the present sample, but an indirect assessment of bone mass by quantitative ultrasound of the heel was performed. Although the mean bone mass in the ICS group appeared to reduce over time, the small sample size and possible inaccuracy of the measurement[41,84] reduced our confidence in interpreting these data. Whether the observed changes in markers of bone turnover observed were clinically important remains to be established. Present knowledge of bone mineral density in children receiving long-term treatment with ICS is still limited and further long-term studies, particularly in young children, would be informative.

Symptom control

There were no significant differences with regard to symptom control and use of rescue bronchodilators between the groups after 6 months of treatment, with equal reduction in episodes of wheeze and night-time cough further supporting the conclusion that early intervention was not beneficial with regard to symptoms within this young population. Although it has been suggested that diary scores may be inaccurate in the assessment of symptom severity and night-time cough,[88] the present results do parallel the results of the lung function measurements. In both study groups there was a time-related improvement in symptoms. The fact that early introduction of ICS showed no significant improvements over symptomatic treatment only may be related to the short time period of the study, as a gradual response to ICS has been previously reported in adults.[114] Alternatively, it may reflect the fact that early anti-inflammatory therapy is not as effective in this young age group as it is in late childhood and early adulthood.

QoL

QoL measurements also demonstrated little difference between the two treatment groups, although improvements in symptoms in both groups were reflected in improvements in QoL of caregivers during the 6 months of assessment. Changes in symptoms were also associated with changes in caregiver's QoL, although this does not prove a causative relationship, and further work in this area would be useful. These results indicate that in the pre-school age group, QoL of caregivers should, perhaps, be assessed rather than a child-centred assessment.

Short-term effects

The lack of evidence to support a substantial beneficial effect of early intervention may reflect poor compliance with treatment, because good symptom control often depends on the patient taking regular preventative medication. Although the pragmatic trial design includes any lack of compliance in the overall measure of effectiveness of treatment,[63] short-term effects will be confounded by the extent to which an individual adheres to their medication regimen. However, the present study is similar to previous reports,[115–117] which have found that, even in closely regulated clinical trials, only about 50% of prescribed medication is actually taken. This suggests that we have observed real differences in treatment and not just the effect of poor compliance.

Sample size calculations for a definitive study

Another confounder in the interpretation of the results of this trial is the relatively small sample size. It is possible that the negative effects observed may be reversed by increasing sample size. The data from the pilot study has therefore been used to perform power of study calculations for a definitive study. When deciding the proposed sample size, three issues need be taken into account: statistical power to detect possible benefits; power to detect possible adverse effects; and feasibility within a reasonable budget. The latter indicated that a trial amongst, say, a further 210 children (total 300, including the 90 pilot sample) was realistic within the resources likely to be available, but that a trial nearer 500 children would be very costly.

Other important issues being addressed in the pilot trial were the possible adverse effects of ICS use, particularly on growth and bone development. There was a mean increase in stature of 3.38 (± 1.01) cm in the ICS group compared to 3.99 (± 1.25) cm amongst the controls. The difference of 0.6 cm may well be an overestimate by chance; hence it seems reasonable to detect (or exclude) a 0.4 cm difference in growth velocity between the two groups over 6 months. To do this with 90% power ($p < 0.05$),[72] would require 130 children per group. The size of effect may be greater and thereby increase statistical power as suggested: in a recent short-term study of pre-pubertal children (aged 7 to 9 years – albeit a more restricted age range than proposed for the current study) the mean growth over 7 months was 2.66 cm in the ICS group compared to 3.66 cm in controls, a difference of 1 cm.[32] It is, however, more difficult to estimate the size of any difference which would be identifiable in the longer term, but a trial size of 260 would have 90% power to identify a difference of 0.4 of an SD (1 cm/year), and 80% power to identify a difference of 0.35 of an SD (0.9 cm/year).

With respect to bone metabolism, a randomised, double-blind, placebo-controlled comparison study of 7–9 year old children taking the ICS BDP found the deoxypyridinoline:creatinine ratio to be 22% higher in the placebo group after 3 months.[44] On entry, our control group had a deoxypyridinoline:creatinine ratio of 73.3 (± 6.1) nmol:mmol. A trial with 130 children in each group would therefore have greater than 90% power ($2p < 0.05$) to detect a 20% difference.[72]

Pulmonary function studies of asthmatic children have shown improvements of about 6% in spirometry with ICS.[71] If the age distribution in a definitive trial was similar to that found in the current pilot at the end of a 5-year study, the mean age would be about 8 years. The mean FEV_1 for an 8 year old boy is 1.55 (± 0.199) litres.[118] A trial with 260 children would, therefore, have 90% power to detect a 6% difference in FEV_1 at the 5% level.[72] A difference in tidal breathing parameters in the pre-school age group of 12.5% in $t_{PTEF}:t_E$ has been found between controls and infants with respiratory syncytial virus-proven bronchiolitis.[81] In a study of young children (3–6 years of age), it was found that those with asthma had a $t_{PTEF}:t_E$ that was, on average, 32% lower than healthy volunteers of the same age.[82] In the present study, the mean value of $t_{PTEF}:t_E$ in our control subjects was 29.5 (1.7). A sample of 300 would, therefore, have adequate power (90%) to detect a 12.5% improvement in $t_{PTEF}:t_E$, at the 5% level.[72]

Health economics

With respect to the four aims of the health economic component of this short-term pilot study, it was not possible to calculate a cost-effectiveness ratio since there was no evidence of greater short-term effectiveness in the early prophylaxis arm. However, we did show that it was feasible to collect data retrospectively on the use of NHS resources and prospectively on symptom-free days and absenteeism from the patient diaries. The data collected regarding drug costs and GP consultations were then used as a basis for sample size calculations, although the absence of inpatient admissions in the pilot data caused a problem because it would take very few inpatient admissions to dwarf the estimated difference in costs of prescriptions and GP consultations. However, the outcome measures used would be suitable for making comparisons in terms of cost-effectiveness between interventions aimed at improving asthma management in children. Comparisons with adults would only be possible if it were assumed that, for example, a symptom-free day was of equal value to an adult and a child. The long-term effects of ICS treatment, therefore, still need to be addressed.

Although early asthma prophylaxis increased costs without any improvement in effectiveness, it would be wrong to conclude at this stage that

it is not a cost-effective use of resources because the current study was not designed to establish the cost-effectiveness of early asthma prophylaxis. The sample size was too small too warrant any clear conclusions regarding cost-effectiveness. In order to provide a satisfactory estimate, any future study would need to be much larger and over a longer timescale. A major challenge in any future trial concerns the cost differences in the first 6 months following randomisation to the eventual lifetime cost differences. A follow-up of longer than 6 months would clearly be required in order to provide an adequate basis for identifying the long-term impact of early prophylaxis.

Conclusions

The EASE pilot study has established that a full study using most of the features of the original pragmatic trial design would be feasible and would provide clear answers to the original questions posed. The study recruited 96% of its proposed sample and confirmed the high prevalence of asthma and wheezing illness in the child population. These two facts add weight to the feasibility of recruiting the desired numbers for a definitive trial (i.e. 300 subjects), although the age group under study would be considerably younger than that originally proposed. With a low drop-out rate of 8%, the pilot has emphasised the acceptability and feasibility of implementing the protocols presented within this report. No significant differences were found in growth rates (stature, weight, knemometry) between the two treatments. Pulmonary function did not significantly improve in the older children; however, tidal breathing parameters in the pre-school children were significantly lower (impaired) at 6 months in the ICS group. Although, no significant differences were found between the groups with regard to bone mass development, the ICS group had significantly lower levels of bone turnover at 6 months. Caregivers' QoL improved significantly in both treatment groups over time, but the differences between groups were non-significant. The change in the QoL of caregivers was significantly associated with change in their child's symptoms. Incidence of wheeze and night-time cough reduced equally in both groups; however, night-time symptom scores and use of rescue bronchodilators were only significantly reduced and number of symptom-free days significantly increased in the β_2-only group. As expected, the prescription costs of patients in the prophylaxis arm were higher and there were no significant differences between the two treatment arms in costs of both asthma- and non-asthma-related GP consultations. The three categories of health-care costs combined were significantly higher for patients assigned to the ICS arm, but there were no significant differences between the two arms for any of the effectiveness measures.

Recommendations

The high level of ICS use in young children with recurrent respiratory symptoms could be a cause for concern. The evidence from the present study suggests that a large number of pre-school children are being prescribed a treatment without adequate evidence that the natural history of the disease, at least in the short term, is any better than it would be with symptomatic treatment with β_2-agonist alone (step 1, BGAM[25]). This suggests that many young children presenting in primary care with symptoms suggestive of asthma may be being exposed unnecessarily to possible systemic side-effects of ICS treatment. The short-term effects, particularly with regard to bone turnover, emphasise the need to monitor the long-term risks, costs and benefits of early introduction of ICS, particularly in the pre-school child, and a definitive trial could be undertaken to address these important questions.

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Appendix 1

Study information sheet

EASE study information sheet
Early **A**sthma prophylaxis, natural history,
Skeletal development and **E**conomy (**EASE**)

Asthma is one of the commonest diseases in the UK and epidemiological studies indicate that there is increasing prevalence and morbidity in patients of all ages. It occurs particularly frequently in children, amongst whom its prevalence has risen substantially over the last 25 years. Although children and young people under 16 years of age account for approximately 20% of the UK population, this age group accounts for almost 50% of all cases of asthma in the population at large. A key study in Aberdeen showed that while in 1964 about 4% of primary school children had asthma, in 1989 this had risen to 10%. The evidence suggests that the rise in prevalence is still continuing; recent studies in the Aberdeen area have shown a further increase in prevalence in primary school children, and a study in the Highlands and Skye found no fewer than 14% of children (17% in Skye) to have asthma. It is estimated that asthma now accounts for between 1 and 2% of the total NHS budget in direct costs. There are also large indirect costs, which fall on the families of affected children.

It has been suggested that earlier introduction of inhaled steroids may reduce asthma morbidity, thus reducing hospital admissions and GP consultations. This suggestion is based on recent advances in understanding the underlying inflammatory mechanisms and evidence from clinical studies that early intervention may modify the medium- to long-term course of the disease.

In late 1994, the NHS Research and Development HTA programme Directorate put this important area out to tender, and the Aberdeen consortium along with a group based in London has been commissioned to perform a short-term study involving 6 months of treatment for children presenting with asthma and wheezing illness.

The objective of the study is to establish whether early introduction of inhaled steroids has a significant effect on the subsequent course of wheezing illness in children. Eligible children (from 6 months to 16 years of age) will be identified as they present with histories suggestive of asthma and recurrent wheeze. Enrolled children will be assigned to one of three age cohorts, namely 6 months to 5 years, 6 to 9 years, and 10 to 16 years of age. Once age categorised, a random allocation will be made to either symptomatic therapy with β_2-agonist or to symptomatic treatment and inhaled steroid. After the first assessment children will be reassessed at 3 and 6 months. If the short-term study is shown to be feasible and beneficial, extension to a full 5-year programme will be considered by the NHS.

The trial aims to establish the effects that the early introduction of inhaled steroids have on:
(i) a child's lung function development (with particular reference to airway function)
(ii) a child's physical growth and development
(iii) a child's bone metabolism and bone density
(iv) a child's quality of life and general health status
(v) the cost–benefits of early treatment.

Further information about the study can be obtained from the study director:
Dr Adam Baxter-Jones, Department of Child Health, University of Aberdeen, Foresterhill, Aberdeen, AB9 2ZD. Tel: 01224 404966 or 01224 681818 ext. 52518, email: chl030@abdn.ac.uk

Appendix 2

Study protocol sheet

EASE study protocol sheet
Early **A**sthma prophylaxis, natural history, **S**keletal development and **E**conomy (**EASE**)

The EASE pilot study (funded by the NHS Executive) will identify the short-term (6 months) effects of early asthma/wheeze prophylaxis with inhaled steroids in newly presenting infants and children. The positive and negative effects of such prophylaxis will be studied over the whole span of childhood in order to identify the separate effects of disease from those attributable to treatment, normal growth and maturation. Outcomes will include subjective health and quality of life assessments, objective measures of lung function, linear growth, bone density and metabolism, consumption of health services and cost–benefits of prophylactic compared to symptomatic treatment. The aim of the pilot study is to assess the feasibility of a longer-term study both in terms of the number of subjects presenting and the methods used to collect information. Towards the end of the pilot study a transition phase has been included which ensures an option to move to a longer-term study with increased cohort sizes.

Children will be identified as they present to GPs with histories suggestive of asthma and recurrent wheeze. In order to be eligible, symptoms would have commenced no longer than 6 months before the consultation and all subjects will be naïve to prior prophylactic therapy. Subjects will be stratified according to personal or immediate family history of atopic disease and those with symptoms precipitated by intercurrent mainly upper respiratory tract infection. If they agree to participate in the study, they will then be randomised to receive either symptomatic therapy with β_2-agonist or to symptomatic treatment and inhaled steroids. Three age cohorts will be used, namely 6 months to 5 years, 6 to 9 years, and 10 to 16 years of age. Once recruited into the study, the subjects will be assessed at three consecutive visits, an initial visit and follow-ups at 3 and 6 months. The youngest age group (6 months to 5 years) will be assessed in the Craig Research and Investigation Unit, Royal Aberdeen Children's Hospital (directed by Dr Margaret Fletcher, Senior Research Nurse/ Honorary Lecturer Child Health). The remaining assessments will take place in the general practices or in the children's family home.

At each visit, subjects will have the following assessed:
(i) lung volumes* (FVC, FEV_1, etc.)
(ii) knemometry (children aged 6 months to 5 years)
(iii) standard anthropometry (height, weight, etc.)
(iv) pubertal development (age at menarche and secondary sexual characteristics for girls aged 8 to 16 years, and secondary sexual characteristics for boys aged 10 to 16 years).
(v) overnight timed urine collection (children aged over 3 years)
(vi) broadband ultrasound attenuation of the os calcis (this is a painless procedure taking about 10 minutes with the subject seated with their heel supported comfortably in a scanning box)
(vii) age-adjusted quality of life questionnaires (to be completed by parents (and by child if > 10 years of age)).

During the course of the study the older children (> 10 years of age) will be asked to fill in a self-report asthma health diary (over 14 days). Economic issues will be addressed capturing information from the asthma diary and a retrospective questionnaire administered at 6 months. Validity of such methods will be assessed with information gathered from GPs and from patients' records.

*In infants younger than 18 months, lung volume measurements will be measured with the infant sedated, using the internationally recommended drug Triclofos sodium, at a dose up to a maximum of 150 mg/kg body weight. The responsible investigator, Dr Margaret Fletcher, has used this drug and dosages for many years, in this and other establishments, with no adverse effects on the child.

Appendix 3

Parent/guardian information sheets

Information for patients and parents or guardians
The EASE Study
Infants under 18 months

This information has been prepared to help you to understand why we are doing this research and what would be involved for your baby if you agree to take part. In addition, it outlines how the results will further our understanding of the nature of cough/wheezing in infants, and how it is best treated. As well as reading this information sheet, you should ask the nurses and doctors concerned any questions that will help you to decide whether to join this research study.

If you choose to be involved in the study, you may stop taking part at any stage. Whether or not you decide to enter the study, the care your child receives will not be affected in any way.

What is the aim of this research?

Cough/wheezing is the commonest medical problem seen in children of all ages and seems to be becoming more common. Much research is taking place in order to try to find out the reasons for the increase. The Medical Faculty of the University of Aberdeen has been awarded a grant from the NHS to find out the best way of treating children such as yours. The treatment of cough/wheezing consists of medicines, such as salbutamol (Ventolin) or terbutaline (Bricanyl), which give immediate relief (often called 'relievers'). Other medicines, such as cromoglycate (Intal) or inhaled steroids, such as Becotide, Budesonide or Flixotide, are used on a regular daily basis (often called 'preventers').

Although preventers are essential for children with severe daily symptoms, their use in mild or moderate wheezing is less clear. Recent research has suggested that early use of preventers for periods of a few months might reduce the chances of wheezing continuing to be a problem as the child grows older. Inhaled steroids are rapidly becoming the standard treatment in moderate or severe cough/wheezing at all ages. Many studies in infants and children have shown their benefit. Their wider use in milder disease has not been adequately looked at, which is why we are making measurements of growth and bone development in this study.

The EASE Study is designed to answer the question of whether early treatment with preventers does modify the subsequent course of wheezing illness in infants and children.

What does this involve for your baby?

Your baby has already visited their GP and has been prescribed reliever treatment, either as a tablet, liquid or inhaler. You will also have been asked to return to your GP's practice to attend their practice nurse's clinic with your child. If you agree for your baby to participate in the study, we will ask you to visit the Craig Research and Investigation Unit, Royal Aberdeen Children's Hospital. This unit has all the special equipment that is necessary for measuring infants. We will ask you to bring your baby along to our measurement room for about 3 hours on a date convenient to you. We will provide a taxi to bring you and your baby to the hospital and take you both home again. You will be very welcome to stay with your baby during all the measurements.

We can only measure the size of your baby's lungs and how fast he or she can get air in and out if he or she is asleep. As babies do not fall asleep to order or for very long periods during the day, a syrup called Triclofos that leads to a short natural sleep is used.

The medicine has been used regularly for thousands of babies, both healthy and unwell, for over 30 years without harmful effects. Once he or she is asleep, special stretchy bands will be placed around his or her chest and tummy and a record made onto a computer of his or her breathing. A special clear (not black) facemask connected to some recording equipment will be used to measure your baby's breathing and the size of his or her lungs. During this measurement your baby will be breathing room air for most of the time and pure oxygen for very short periods of time. Oxygen is a vital part of the air we breathe and is not known to cause any ill-effects in children when used for short periods. To measure how easily your baby can make air go in and out of his or her lungs, a little jacket is wrapped around his or her chest and tummy. At the start of a breath out, the jacket is used to give a gentle 'hug' to help get air out faster. None of these tests will upset your baby who is likely to sleep through the whole time, which is usually about 30 to 40 minutes. At the start of the test, we will weigh your baby so that we can decide how much medicine to give. At the end of the test, we will measure your child's length, as the size of the lungs are closely linked to body length. We will also ask you to bring with you a urine sample from your child; arrangements and instructions for urine collection will be explained to you prior to your attendance at the Craig Unit. This sample will allow us to measure some natural chemicals, which reflect your child's bone growth. A measurement of length from his or her knee to heel will be taken using a special ruler, which measures length very accurately. This measurement will be done on your initial visit and weekly for a further 4 weeks. These four lengths can be done in your own home to save you from travelling to the hospital. A measure of thickness of the heel bone will also be made using an ultrasound method, which is simple, quick and painless, involving no X-rays or radiation.

After these tests, your child will continue using the reliever treatment and may be given preventer treatment as well, in the form of an inhaler taken twice a day. All the measurements described above will be repeated after a further 3 and 6 months. During the course of the study, we will ask you to fill in some questionnaires describing your child's daily health and activity. After 6 months, your GP will reassess your child and, depending on how well controlled their cough/wheeze is, will follow current asthma treatment guidelines to either step up or step down treatment.

Are there any risks or discomforts for your child?

All of the measurements in this study involve no discomfort. The medical treatments being used are well established in the treatment of cough/wheezing illness in infants and children.

Who will this help?

Taking part in this research may not benefit your child directly but the overall objective is to identify the best way of treating children with cough/wheezing illness in its early stages.

What will happen to the information you provide?

This will be treated in strict confidence and will only be used for research in a way that will not allow you ever to be identified. Your family details (name and address) will not be stored on a computer database.

Who can I contact about this research?

Please ask Miss Nicky Sim about any aspect of this study if you would like to know more. She can be contacted at or through the Craig Research and Investigation Unit, Royal Aberdeen Children's Hospital, Tel: 01224 681818 ext. 52036.

If you have any more questions about the research, your rights as a participant or what to do in the event of an injury or claim contact Mrs M Dow, Tel: 01224 404461, who will be happy to answer any questions or will direct you to someone who can provide you with more information.

Information for patients and parents or guardians
The EASE Study
Children 18 months to 6 years

This information has been prepared to help you to understand why we are doing this research and what would be involved for your child if you agree to take part. In addition, it outlines how the results will further our understanding of the nature of cough/wheezing, and how it is best treated. As well as reading this information sheet, you should ask the nurses and doctors concerned any questions that will help you to decide whether to join this research study.

If you choose to be involved in the study, you may stop taking part at any stage. Whether or not you decide to enter the study, the care your child receives will not be affected in any way.

What is the aim of this research?

Cough/wheezing is the commonest medical problem seen in children of all ages and seems to be becoming more common. Much research is taking place in order to try to find out the reasons for the increase. The Medical Faculty of the University of Aberdeen has been awarded a grant from the NHS to find out the best way of treating children such as yours. The treatment of cough/wheezing consists of medicines, such as salbutamol (Ventolin) or terbutaline (Bricanyl), which give immediate relief (often called 'relievers'). Other medicines, such as cromoglycate (Intal) or inhaled steroids, such as Becotide, Budesonide or Flixotide, are used on a regular daily basis (often called 'preventers').

Although preventers are essential for children with severe daily symptoms, their use in mild or moderate wheezing is less clear. Recent research has suggested that early use of preventers for periods of a few months might reduce the chances of wheezing continuing to be a problem as the child grows older. Inhaled steroids are rapidly becoming the standard treatment in moderate or severe asthma at all ages. Many studies in infants and children have shown their benefit. Their wider use in milder disease has not been adequately looked at, which is why we are making measurements of growth and bone development in this study.

The EASE Study is designed to answer the question of whether early treatment with preventers does modify the subsequent course of wheezing illness in infants and children, and to address the concerns of parents and healthcare professionals regarding steroid safety.

What does this involve for your child?

Your child has already visited their GP and has been prescribed reliever treatment either as a tablet, liquid or inhaler. You will also have been asked to return to your GP's practice to attend their practice nurse's clinic with your child. If you agree for your child to participate in the EASE Study, your child will be randomly chosen to either continue with their current reliever treatment or alternatively be prescribed preventer treatment as well. We will ask you to visit the Craig Research and Investigation Unit, Royal Aberdeen Children's Hospital. This unit has all the special equipment that is necessary for measuring infants. We will ask you to bring your child along to our measurement room on a date arranged with you. We will provide a taxi to bring you and your child to the hospital and take you both home again. You will be very welcome to stay with your child during all the measurements.

We can only measure the size of your child's lungs and how fast he or she can get air in and out if he or she is breathing quietly. For older children, we have a selection of videos for your child to watch and they will hopefully sit quietly for long enough for us to obtain these measurements. At this age, it is difficult to predict how much a child can manage, so we aim to achieve what we can and accept some children cannot manage until a little older. We place stretchy bands around his or her chest and tummy

and a recording is made onto a computer. If your child is 3 years and above, we will use a special clear (not black) facemask connected to some recording equipment. This will only be done if your child is happy to wear it. During this measurement, your child will be breathing room air for most of the time and pure oxygen for very short periods of time. Oxygen is a vital part of the air we breathe and is not known to cause any ill-effects in children when used for short periods. At the end of the test, we will measure your child's length, as the size of the lungs are closely linked to body length. We will also ask you to bring with you a urine sample from your child; arrangements and instructions for urine collection will be explained to you prior to your attendance at the Craig Unit. This sample will allow us to measure some natural chemicals, which reflect your child's bone growth. A measure of thickness of the heel bone will also be made using an ultrasound method, which is simple, quick and painless, involving no X-rays or radiation.

All the measurements described above will be repeated at 6-month intervals for 4 years. During the course of the study we will ask you to fill in some questionnaires describing your child's daily health and activities, and any influences these have on your child's school attendance. When your child has reached 5 years, we will perform a skin prick test to see if they are sensitive to house dust mite, pollen or cat/dog hair. This test is only performed once during the course of the study.

Six months into the study, your GP will reassess your child and, depending on how well controlled their cough/wheeze is, will follow current asthma treatment guidelines to either step up or step down treatment.

Are there any risks or discomforts for your child?

All of the measurements in this study involve no discomfort. The medical treatments being used are well established in the treatment of cough/wheezing illness in infants and children.

Who will this help?

Taking part in this research may not benefit your child directly but the overall objective is to identify the best way of treating children with cough/wheezing illness in its early stages.

What will happen to the information you provide?

This will be treated in strict confidence and will only be used for research in a way that will not allow you ever to be identified. Your family details (name and address) will not be stored on a computer database.

Who can I contact about this research?

Study Director — Dr Adam Baxter-Jones, Department of Child Health, University of Aberdeen, Foresterhill, Aberdeen. Tel: 01224 404966, Fax: 01224 663658, email: baxter.jones@abdn.ac.uk.

Research Nurses — Ms Nicky Sim, Ms Anne Baird and Mrs Joanna Gordon. Tel: 01224 404966 or through the Craig Research and Investigation Unit, Royal Aberdeen Children's Hospital, Tel: 01224 681818 ext. 52036.

If you have any more questions about the research, your rights as a participant, or what to do in the event of an injury or claim, please contact Mrs M Dow, Tel: 01224 404461, who will be happy to answer any questions or will direct you to someone who can provide you with more information.

Information for patients and parents or guardians
The EASE Study
Children above 6 years

This information has been prepared to help you to understand why we are doing this research and what would be involved for your child if you agree to take part. In addition, it outlines how the results will further our understanding of the nature of cough/wheezing illness, and how it is best treated. As well as reading this information sheet, you should ask the nurses and doctors concerned any questions that will help you to decide whether to join this research study.

If you choose to be involved in the study, you may stop taking part at any stage. Whether or not you decide to enter the study, the care your child receives will not be affected in any way.

What is the aim of this research?

Cough/wheezing is the commonest medical problem seen in children of all ages and seems to be becoming more common. Much research is taking place in order to try to find out the reasons for the increase. The Medical Faculty of the University of Aberdeen has been awarded a grant from the NHS to find out the best way of treating children such as yours. The treatment of cough/wheezing consists of medicines, such as salbutamol (Ventolin) or terbutaline (Bricanyl), which give immediate relief (often called 'relievers'). Other medicines, such as cromoglycate (Intal) or inhaled steroids, such as Becotide, Budesonide or Flixotide, are used on a regular daily basis (often called 'preventers').

Although preventers are essential for children with severe daily symptoms, their use in mild or moderate wheezing is less clear. Recent research has suggested that early use of preventers for periods of a few months might reduce the chances of wheezing continuing to be a problem as the child grows older. Inhaled steroids are rapidly becoming the standard treatment in moderate or severe asthma at all ages. Many studies in infants and children have shown their benefit. However, their wider use in milder disease has not been adequately investigated.

The EASE Study is designed to answer the question of whether early treatment with preventers does modify the subsequent course of wheezing illness in infants and children and to address the concerns of parents and healthcare professionals regarding steroid safety.

What does this involve for your child?

Your child has already visited their GP and has been prescribed reliever treatment, either as a tablet, liquid or inhaler. You will also have been asked to return to your GP's practice to attend their practice nurse's clinic. If you agree for your child to participate in the EASE Study, your child will be randomly chosen to either continue with their current reliever treatment or alternatively be prescribed preventer treatment as well. When you come to the practice nurse's clinic, we will measure your child's growth (height and weight (older children will also be assessed for pubertal development)), and their lung function, measured by blowing into a tube. We will also ask you to bring with you a urine sample from your child; arrangements and instructions for urine collection will be explained to you prior to your attendance of the practice nurse's clinic by one of the EASE Study nurses. This urine sample will allow us to measure some natural chemicals, which reflect your child's bone growth. A measure of thickness of the heel bone will also be made using an ultrasound method, which is simple, quick and painless, involving no X-rays or radiation.

All the measurements described above will be repeated at 6-month intervals for 4 years. During the course of the study, we will ask you to fill in some questionnaires describing your child's daily health and activities, and any influences these have on your child's school attendance. Once during the course of the study, we

will perform a skin prick test on your child to see if they are sensitive to house dust mite, pollen or cat/dog hair.

Six months into the study, your GP will reassess your child and, depending on how well controlled their cough/wheeze is, will follow current asthma treatment guidelines to either step up or step down treatment.

Are there any risks or discomforts for your child?

All of the measurements in this study involve no discomfort. The medical treatments being used are well established in the treatment of cough/wheezing illness in infants and children.

Who will this help?

Taking part in this research may not benefit your child directly but the overall objective is to identify the best way of treating children with cough/wheezing illness in its early stages.

What will happen to the information you provide?

This will be treated in strict confidence and will only be used for research in a way that will not allow you ever to be identified. Your family details (name and address) will not be stored on a computer database after the study is completed. All family details will be kept apart from any medical information.

Who can I contact about this research?

Study Director Dr Adam Baxter-Jones, Department of Child Health, University of Aberdeen, Foresterhill, Aberdeen. Tel: 01224 404966, Fax: 01224 663658, email: baxter.jones@abdn.ac.uk.

Research Nurses Ms Nicky Sim, Ms Anne Baird and Mrs Joanna Gordon. Tel: 01224 404966 or through the Craig Research and Investigation Unit, Royal Aberdeen Children's Hospital, Tel: 01224 681818 ext. 52036.

World Wide Web Page Address http://www.abdn.ac.uk/child_health/ease.htm

If you have any more questions about the research, your rights as a participant, or what to do in the event of an injury or claim please contact Mrs M Dow, tel: 01224 404461, who will be happy to answer any questions or will direct you to someone who can provide you with more information.

Appendix 4

Informed consent forms

EASE Study consent form

Parent/guardian

Name of child: .....

Name of study: Early asthma prophylaxis, natural history, skeletal development and economy (EASE) study

Principal investigator: Dr Adam Baxter-Jones, Research Fellow
Professor P Helms, Consultant Paediatrician

I have read the parent/guardian information sheet on the above study and have had the opportunity to discuss the details with ..... and ask questions. The nature and purpose of the tests to be undertaken have been explained to me. I understand fully what is proposed to be done.

I am happy for my child to take part in the study as it has been outlined to me, but I understand that I am completely free to withdraw my child from the study, or any part of the study, at any time I wish, and that this will not affect my child's continuing medical treatment in any way.

I understand that these trials are part of a research project designed to promote medical knowledge, which has been approved by the Joint Ethical Committee, and may be of no benefit to my child.

I hereby fully and freely consent for my child to participate in the study, which has been fully explained to me.

Signature of parent/guardian: .....

Date: __ __ / __ __ / 19 __ __

I confirm that I have explained to ..... parent/guardian, the nature and purpose of the tests to be undertaken.

Signature of investigator: .....

Date: __ __ / __ __ / 19 __ __

Please note: This form must be kept in the patient's notes

EASE Study consent form

Subject

Name: .....

Name of study: Early asthma prophylaxis, natural history, skeletal development and economy (EASE) study

Principal investigator: Dr Adam Baxter-Jones, Research Fellow
Professor P Helms, Consultant Paediatrician

I have read the subject information sheet on the above study and have had the opportunity to discuss the details with ..... and ask questions. The nature and purpose of the tests to be undertaken have been explained to me. I understand fully what is proposed to be done.

I am to take part in the study as it has been outlined to me, but I understand that I am completely free to withdraw from the study, or any part of the study, at any time I wish, and that this will not affect my continuing medical treatment in any way.

I understand that these trials are part of a research project designed to promote medical knowledge, which has been approved by the Joint Ethical Committee, and may be of no benefit to myself.

I hereby fully and freely consent to participate in the study, which has been fully explained to me.

Signature: .....

Date: __ __ / __ __ / 19 __ __

I confirm that I have explained to ..... the nature and purpose of the tests to be undertaken.

Signature of investigator: .....

Date: __ __ / __ __ / 19 __ __

Please note: This form must be kept in the patient's notes

Appendix 5

GP letters

‹‹Date››

‹‹Title›› ‹‹Last name››
‹‹Company››
‹‹Address 1››
‹‹Address 2››
‹‹City››
‹‹Postal code››

Dear ‹‹Title›› ‹‹Last name››

Thank you again for your cooperation in the EASE Study.

This letter is to inform you that xxx has entered the study and was randomised to receive steroid treatment for 6 months from the above date.

As discussed previously, brand name and device is left to your discretion. Please prescribe either (twice daily) (i) dry powder inhaler 200 µg Becotide, 200 µg Budesonide or 100 µg Fluticasone, or (ii) a spacer (with or without facemask) 200 µg Becotide, 200 µg Budesonide or 100 µg Fluticasone.

At the end of the 6-month assessment phase we will contact you again and it is then recommended that the British Guidelines on Asthma Management are followed to either reduce or step up steroid dosage.

Please contact me at the above if any further information is needed.

Yours sincerely

Dr Adam Baxter-Jones
Study Director

‹‹Date››

‹‹Title›› ‹‹Last name››
‹‹Company››
‹‹Address 1››
‹‹Address 2››
‹‹City››
‹‹Postal code››

Dear ‹‹Title›› ‹‹Last name››

This letter is to inform you that xxx has entered the study and was randomised to continue with β_2-agonist treatment for 6 months from the above date.

At the end of the 6-month assessment phase, we will contact you again and it is then recommended that British Guidelines on Asthma Management are followed with regard to control of symptoms. As discussed previously, if additional treatment is needed during the assessment phase, this will not affect their continued involvement in the study.

Please contact me at the above if any further information is needed.

Thank you again for your cooperation with us in the EASE Study.

Yours sincerely

Dr Adam Baxter-Jones
Study Director

‹‹Date››

‹‹Title›› ‹‹Last name››
‹‹Company››
‹‹Address 1››
‹‹Address 2››
‹‹City››
‹‹Postal code››

Dear ‹‹Title›› ‹‹Last name››

We are writing to inform you that xxx has completed the initial 6-month period on the EASE Study, during which time he/she was randomised to receive inhaled steroids according to the protocol. As previously discussed, we now recommend that you bring xxx in for reassessment of treatment according to the British Guidelines on Asthma Management.

We will advise you as to any EASE follow-up visits for xxx, and keep you up to date with the development of the study. In the meantime, may we thank you for your continuing cooperation in the EASE Study.

Yours sincerely

Dr Adam Baxter-Jones
Study Director

‹‹Date››

‹‹Title›› ‹‹Last name››
‹‹Company››
‹‹Address 1››
‹‹Address 2››
‹‹City››
‹‹Postal code››

Dear ‹‹Title›› ‹‹Last name››

This letter is to inform you that xxx has completed the initial 6-month period on the EASE Study, having been randomised to continue with fl2-agonist treatment only. As previously discussed, we now recommend that you bring xxx in for reassessment of xxx asthma control.

We will advise you as to any EASE follow-up visits for xxx, and keep you up to date with the development of the study. In the meantime, may we thank you for your continuing cooperation in the EASE Study.

Yours sincerely

Dr Adam Baxter-Jones
Study Director

Appendix 6

Results sheets

Randomisation result

1. Child's name: .....

2. Study number: __ __ __ __

3. Steroid treatment (circle one): Yes or No

4. Steroid brand name: .....

5. Daily dosage: __ __ __ µg/day

6. Delivery device: .....

7. Date commenced: __ __ / __ __ / 19 __ __

8. List other prophylactic therapy:

(i) .....

(ii) .....

(iii) .....

Craig Unit 0 to 18 months

Name: ..... Study number: __ __ __ __

Measurement date: __ __ /__ __ /19__ __

Visit number (1..3): __

1.0 **Anthropometry**

1.1 Length (1st): __ __ . __ cm 1.2 Length (2nd): __ __ . __ cm

1.3 Weight: __ __ . __ kg

1.4 Knemometry: __ __ __ . __ __ mm 1.5 Knemometry: SD 0.__ __

1.4.1 (please circle): Walking / Crawling / Sitting

2.0 **Lung function**

2.1 t_{PTEF}:t_E: __ . __ __ __ 2.2 RR: __ __ . __ /minute

2.3 FRC: __ __ __ . __ ml 2.4 LCI: __ __ . __

3.0 **Urine collection** OVERNIGHT / SPOT

3.0.1 If SPOT, time sample taken: __ __ : __ __ (use 24-hour clock)

3.1 Volume: __ __ __ ml

3.2 Time commenced: __ __ : __ __ p.m.

3.3 Time completed: __ __ : __ __ a.m.

3.4 Night-time sample YES/NO 3.5 Morning sample YES/NO

5.0 **Questionnaires**

	Completed
5.1 Health status	YES/NO
5.2 Caregiver's	YES/NO
5.3 Physical activity	YES/NO
5.4 Quality of life (form A, B or C)	YES/NO

6.0 **Asthma diary** YES/NO

Craig Unit 18 months to 5 years

Name: ..... Study number: __ __ __ __

Measurement date: __ __ /__ __ /19__ __

Visit number (1..3): __

1.0 **Anthropometry**

1.1 Height (1st): __ __ . __ cm 1.2 Height (2nd): __ __ . __ cm

1.3 Weight: __ __ . __ kg

1.4 Knemometry: __ __ __ . __ __ mm 1.5 Knemometry SD 0.__ __

1.4.1 (please circle) Walking / Crawling / Sitting

2.0 **Lung function**

2.1 t_{PTEF}:t_E: __ . __ __ __ 2.2 RR: __ __ . __ /minute

2.3 Number of breaths: __ __

2.4 FRC: __ __ __ . __ ml 2.5 LCI: __ __ . __

3.0 **Urine collection** OVERNIGHT / SPOT

3.0.1 If SPOT, time sample taken: __ __ : __ __ (use 24-hour clock)

3.1 Volume: __ __ __ ml

3.2 Time commenced: __ __ : __ __ p.m.

3.3 Time completed: __ __ : __ __ a.m.

3.4 Night-time sample YES/NO 3.5 Morning sample YES/NO

5.0 **Questionnaires**

		Completed
5.1	Health status	YES/NO
5.2	Caregiver's	YES/NO
5.3	Physical activity	YES/NO
5.4	Quality of life (form A, B or C)	YES/NO

6.0 **Asthma diary** YES/NO

Female

Name: ..... Study number: .....

Measurement date: __ __ /__ __ /19__ __

Visit number (1..3): __

1.0 **Anthropometry**

1.1 Height (1st): __ __ __ . __ cm 1.2 Height (2nd): __ __ __ . __ cm

1.3 Weight: __ __ . __ kg

Pubertal ratings

		Stage (circle)
1.4	Breast	1 2 3 4 5
1.5	Menarche	YES/NO

If yes, month and year of 1st menstrual period: Month __ __ __ Year __ __

2.0 **Spirometry**

2.1 FVC: __ . __ __ litres 2.2 FEV_1: __ . __ __ litres

2.3 PEFR: __ __ __ 2.4 Maximal effort: YES/NO

3.0 **Urine collection**

3.1 Volume: __ __ __ ml

3.2 Time commenced: __ __ : __ __ p.m.

3.3 Time completed: __ __ : __ __ a.m.

3.4 Night-time sample YES/NO 3.5 Morning sample YES/NO

4.0 **Bone mass – left heel**

4.1 BUA: __ __ __ db/MHz 4.2 VOS: __ __ __ m/second
4.3 BUA: __ __ __ db/MHz 4.4 VOS: __ __ __ m/second
4.4 BUA: __ __ __ db/MHz 4.5 VOS: __ __ __ m/second

5.0 **Questionnaires**

		Completed
5.1	Health status	YES/NO
5.2	Caregiver's	YES/NO
5.3	Physical activity	YES/NO
5.4	Quality of life (form A, B or C)	YES/NO

6.0 **Asthma diary** YES/NO

Male

Name: ..... Study number: .....

Measurement date: __ __ /__ __ /19__ __

Visit number (1..3): __

1.0 **Anthropometry**

1.1 Height (1st): __ __ __ . __ cm 1.2 Height (2nd): __ __ __ . __ cm

1.3 Weight: __ __ . __ kg

Pubertal ratings

		Stage (circle)
1.4	Genitalia	1 2 3 4 5
1.5	Pubic hair	1 2 3 4 5
1.6	Axillary hair	1 2 3

2.0 **Spirometry**

2.1 FVC: __ . __ __ litres 2.2 FEV_1: __ . __ __ litres

2.3 PEFR: __ __ __ 2.4 Maximal effort: YES/NO

3.0 **Urine collection**

3.1 Volume: __ __ __ ml

3.2 Time commenced: __ __ : __ __ p.m.

3.3 Time completed: __ __ : __ __ a.m.

3.4 Night-time sample YES/NO 3.5 Morning sample YES/NO

4.0 **Bone mass – left heel**

4.1 BUA: __ __ __ db/MHz 4.2 VOS: __ __ __ m/second

4.3 BUA: __ __ __ db/MHz 4.4 VOS: __ __ __ m/second

4.4 BUA: __ __ __ db/MHz 4.5 VOS: __ __ __ m/second

5.0 **Questionnaires**

		Completed
5.1	Health status	YES/NO
5.2	Caregiver's	YES/NO
5.3	Physical activity	YES/NO
5.4	Quality of life (form A, B or C)	YES/NO

6.0 **Asthma diary** YES/NO

Overnight urine collection

A. Child's name: ..... B. Study number: __ __ __ __

C. Visit number (1..3): __ D. Date: __ __ / __ __ /19 __ __

Instructions

1. Empty the bladder prior to going to bed (into the jug provided)
2. Note the time when bladder was emptied Time: __ __ : __ __ p.m.
3. Pour a sample of the urine, from the jug into container A (small collecting tube), fill it about three-quarters full
4. Discard the rest of the urine
5. Collect any urine passed overnight (again using jug provided) and pour into collecting bottle B (500 ml sealed bottle)
6. In the morning collect ALL the urine passed first thing and pour into collecting bottle B (adding to any collected overnight) and note the time Time: __ __ : __ __ a.m.

Note:

(1) Please keep the urine as cool as possible prior to bringing it to the asthma clinic

(2) Let us know if you have any problems, i.e. spillage, as the exact volume must be known for accurate assessment

Economic evaluation – from patient records during first 6 months

Name: ..... Study number: .....

1. 1st visit date: _ _ _/ _ _ _ / _ _ 2. 3rd visit date: _ _ _/ _ _ _ / _ _

3. Number of prescriptions Total number = _____

	Prescription (drug and dosage)		Prescription (drug and dosage)
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

4. Number of GP visits
(code: 1 = GP surgery, 2 = Patient's home, 3 = General practice on-call doctors, 4 = Elsewhere, 5 = Practice nurse)

Asthma/wheeze-related	Non-asthma/wheeze-related

5. Number of A & E visits: _____

6. Number of hospital outpatient visits

Asthma/wheeze-related	Non-asthma/wheeze-related

7. Number of hospital inpatient stays: _____

Date of admission	Length of stay (days)

8. Any other specific tests requested by GP

1	
2	
3	

Appendix 7

Calibration procedures

Anthropometers

The distance between the base of the instrument and the measuring arm was measured using a steel rod of known length and compared to the digital read out. This was performed prior to the measurement session.

Spirometer

The spirometer was calibrated, prior to each testing session, following the calibration procedures outlined in the instrumentation manual (2120 Storage Spiromter User Manual, Vitalograph Ltd). This was a step-wise procedure prompted by instructions in the software menu. A Vitalograph precision 1 litre syringe was used.

Bone densatometer

Although a precision instrument, the calibration of the CUBA was checked prior to each testing session against the BUA and VOS Phantom provided with the system. The Phantom had a known BUA and VOS.

Appendix 8

Self-report questionnaires

Health status and Family history

Visit 1

Instructions

1. Printed on the next few pages are a number of questions about the health of your child and your family.
2. If you don't understand something, then please ask the nurse present and she will help you.
3. Each answer is completely confidential and will not be shown to anyone else. Answers will be stored on computer by study number; no names or addresses will be entered.
4. Please make sure that you have answered ALL the questions.

SECTION 1: Biographical details

1.1 Child's study number: __ __ __ __

1.2 Today's date: __ __ / __ __ /19 __ __ 1.2.1 Visit number (1..3): 1

1.3 Name of person completing this form: .....

1.3.1 Relationship to child: .....

1.4 Contact details:

1.4.1 Current address: .....

.....

Postcode: .....

1.4.2 Telephone number: Home ...../.....

(STD code)

1.4.3 Work ...../.....

(STD code)

1.5 **Parental information**

Mother

1.5.1 Height: Measured: __ __ __ . __ cm

1.5.2 Reported: __ __ __ . __ cm or __ ft ___ in

1.5.3 Age of menarche: __ __ years __ __ months

Father

1.5.4 Height: Measured: __ __ __ . __ cm

1.5.5 Reported: __ __ __ . __ cm or __ ft ___ in

1.6 Child's information

1.6.1 Surname: .....

1.6.2 First name: ..... 1.6.3 Other initials: .....

1.6.4 Sex (please circle one): Male/Female

1.6.5 Date of birth: __ __ / __ __ /19 __ __

1.6.6 Birth weight: __ . __ __ kg or 1.6.6.1 __ __ lb __ __ oz

1.6.7 Was he/she born early? Yes/No

1.6.7.1 If Yes, how many weeks before he/she was due? __ __ weeks

1.6.8 Did he/she require special care or ventilation after he/she was born? Yes/No

1.6.9 Child's birth order (please circle one): 1st 2nd 3rd 4th Other .....

SECTION 2: Child's health status

1. How many attacks of wheezing has your child had in the past 12 months?

   None ☐

   1 to 3 ☐

   4 to 12 ☐

   More than 12 ☐

2. On average how long do these attacks last? ..... minutes

3. In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?

   Never woken with wheezing ☐

   Less than once per month ☐

   Less than one night per week ☐

   One or more nights per week ☐

4. In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?

   Yes ☐
   No ☐

IF YOU HAVE ANSWERED 'NO', PLEASE SKIP TO QUESTION 6.

5. In the last 12 months, how often, on average, has your child's sleep been disturbed due to coughing?

   Never woken with coughing ☐

   Less than one night per week ☐

   One or more nights per week ☐

6. In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths, or to make it difficult for your child to drink?

Yes	☐
No	☐

7. In the last 12 months, has your child ever coughed or wheezed as a result of:

		Cough		Wheeze	
		Yes	No	Yes	No
(a)	Colds				
(b)	Contact with furry animals				
(c)	Contact with cigarette smoke				
(d)	Emotion (laughing, crying, excitement)				
(e)	Exercise				

8. Do these attacks occur more frequently at a particular time of year?

Yes	☐
No	☐

If Yes, when?

Spring	☐
Summer	☐
Autumn	☐
Winter	☐

9. In the last 12 months, has your child received any medication for wheeze or cough?

Yes	☐
No	☐

IF YOU HAVE ANSWERED 'NO', PLEASE SKIP TO QUESTION 11.

10. Please write down any treatment used for cough/wheeze, in the last 12 months
    (a) those given when needed for wheeze or cough
    (b) those given regularly, i.e. every day

(a) Given when needed for wheeze or cough

Name of treatment	Strength (written on inhaler or bottle)	Dose (number of puffs or tablets)	Number of times used a day when symptoms present

(b) Given regularly, i.e. every day

Name of treatment	Strength (written on inhaler or bottle)	Dose (number of puffs or tablets)	Number of times per day

11. Has your child ever had a problem with sneezing, or a runny or blocked nose when he/she DID NOT have a cold or the flu?

Never	☐
In the past 12 months	☐
More than 1 year ago	☐

IF YOU HAVE ANSWERED 'NEVER', PLEASE SKIP TO QUESTION 14.

12. In the past 12 months, was this nose problem accompanied by itchy-watery eyes?

Yes ☐
No ☐

IF YOU HAVE ANSWERED 'NO', PLEASE SKIP TO QUESTION 14.

13. In the last 12 months, has your child received any medication for this nose/eye problem?

Yes ☐
No ☐

If Yes, what medication was used? .....

14. Has your child ever had an itchy rash which was coming and going for at least 6 months or been told it was eczema?

Never ☐
In the past 12 months ☐
More than 1 year ago ☐

IF YOU HAVE ANSWERED 'NEVER', PLEASE SKIP TO QUESTION 18.

15. Has this itchy rash at any time affected any of the following places:

The folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

Yes ☐
No ☐

16. At what age did this itchy rash first occur?

Under 1 year ☐

Age 1–2 years ☐

Age 2 or more ☐

17. In the last 12 months, has your child received any medication for this rash?

Yes ☐
No ☐

If Yes, what medication was used? .....

SECTION 3: Family information

THE NEXT FEW QUESTIONS ASK FOR INFORMATION ABOUT YOURSELF AND YOUR FAMILY

18. Who, apart from your child, lives at home? Please write below the relationship to the child and ages of all other household members (include yourself).

First and last name and relationship to child (e.g. brother, sister, grandparent, lodger) **Age**

....

....

....

....

....

....

19. Do any of these household members smoke at home?

Yes ☐
No ☐

If Yes, who and how many cigarettes smoked at home?

Name	**Number of cigarettes smoked/day (please tick in the relevant box)**		
	1–10 per day	11–20 per day	More than 20 per day

20. Do you have any furry pets at home?

Yes ☐
No ☐

If Yes, what kind and how many?

What kind of pet	**How many**
.....	.....
.....	.....
.....	.....
.....	.....

SECTION 4: About yourself

21. Have you ever had, or been told that you had, asthma?

Yes ☐
No ☐

IF YOU HAVE ANSWERED 'NO', PLEASE SKIP TO QUESTION 24.

22. Do you still have asthma?

Yes ☐
No ☐

If you have answered 'No', at what age did your asthma stop? __ __ years

23. Do you still take medicine or treatment for asthma?

Yes ☐
No ☐

24. Have you ever had, or been told that you had hay fever?

Yes ☐
No ☐

IF YOU HAVE ANSWERED 'NO', PLEASE SKIP TO QUESTION 27.

25. Do you still have hay fever?

Yes ☐
No ☐

If you have answered 'No', at what age did your hay fever stop? __ __ years

26. Do you still take medicine or treatment for hay fever?

Yes ☐
No ☐

27. Have you ever had, or been told that you had eczema?

Yes ☐
No ☐

IF YOU HAVE ANSWERED 'NO', PLEASE SKIP TO QUESTION 30.

28. Do you still have eczema?

Yes ☐
No ☐

If you have answered 'No', at what age did your eczema stop? __ __ years

29. Do you still take medicine or treatment for eczema?

Yes ☐
No ☐

SECTION 5: About the child's other parent

30. Has the child's other parent ever had, or been told that they had asthma?

Yes ☐
No ☐

IF YOU HAVE ANSWERED 'NO', PLEASE SKIP TO QUESTION 33.

31. Do they still have asthma?

Yes ☐
No ☐

If you have answered 'No', at what age did their asthma stop? __ __ years

32. Do they still take medicine or treatment for asthma?

Yes ☐
No ☐

33. Has the child's other parent ever had, or been told that they had hay fever?

Yes ☐
No ☐

IF YOU HAVE ANSWERED 'NO', PLEASE SKIP TO QUESTION 36.

34. Do they still have hay fever?

Yes ☐
No ☐

If you have answered 'No', at what age did their hay fever stop? __ __ years

35. Do they still take medicine or treatment for hay fever?

Yes ☐
No ☐

36. Has the child's other parent ever had, or been told that they had eczema?

Yes ☐
No ☐

IF YOU HAVE ANSWERED 'NO', PLEASE SKIP TO QUESTION 39.

37. Do they <u>still</u> have eczema?

Yes ☐
No ☐

If you have answered 'No', at what age did their eczema stop? __ __ years

38. Do they still take medicine or treatment for eczema?

Yes ☐
No ☐

39. Do you have any other children?

Yes ☐
No ☐

IF YOU HAVE ANSWERED 'YES', PLEASE TURN OVER THE PAGE TO QUESTION 40

IF YOU HAVE ANSWERED 'NO' TO QUESTION 39, YOU HAVE NOW FINISHED THE QUESTIONNAIRE

THANK YOU VERY MUCH FOR YOUR TIME

SECTION 6: About your other children

40. For each child:

A. Name ..... Age .....

Does he/she have asthma?	Yes/No
This child's birth weight? (if you can remember)	..... kg or ..... lb ..... oz
Was this child born early, and if so how many weeks before he/she was due?	Yes/No ..... weeks
Did this child require special care or ventilation after he/she was born?	Yes/No

B. Name ..... Age .....

Does he/she have asthma?	Yes/No
This child's birth weight? (if you can remember)	..... kg or ..... lb ..... oz
Was this child born early, and if so how many weeks before he/she was due?	Yes/No ..... weeks
Did this child require special care or ventilation after he/she was born?	Yes/No

C. Name ..... Age .....

Does he/she have asthma?	Yes/No
This child's birth weight? (if you can remember)	..... kg or ..... lb ..... oz
Was this child born early, and if so how many weeks before he/she was due?	Yes/No ..... weeks
Did this child require special care or ventilation after he/she was born?	Yes/No

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This report was identified as a priority by the Pharmaceutical Panel.

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We look forward to hearing from you.

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