

Early introduction of inhaled steroids in wheezing children presenting in primary care. A pilot study

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Abstract

Background Recurrent wheezing illness in childhood is a frequent reason for consultation in both primary and secondary care and whilst there is widespread support for the earlier introduction of inhaled corticosteroids (ICS) concerns remain about potential adverse systemic effects.

Objective We sought to identify the feasibility and size of study required to assess the benefits, adverse effects and cost-effectiveness of early introduction of ICS.

Methods We entered 86 children (mean age 4.5 years) with at least two consecutive wheezing episodes into a pragmatic randomized controlled trial. All children were already being prescribed β_2 -agonist and those allocated to ICS were prescribed twice daily beclomethasone dipropionate 200 μ g or budesonide 200 μ g. At entry and 3 and 6 months age appropriate lung function (FEV_1 , $T_{ptef:T_e}$), respiratory symptoms, quality of life of children and carers, growth and sexual maturation, bone mass and bone turnover, and health care costs were assessed.

Results Drop out rate was 8% (7 of 86). No significant differences were found in FEV_1 or $T_{ptef:T_e}$ at 6 months. Respiratory symptoms and health-related quality of life of children and carers improved equally in both groups. No significant differences were found in growth rates or in bone mass. In the ICS group markers of bone turnover (Pyd:Cr) fell (271 vs 237 nmol/mmol) in contrast to a rise in those on β_2 alone (255 vs 319 nmol/mmol) $P < 0.05$. Combined health care costs were higher in the ICS group.

Conclusions The low drop out rate provided evidence that the protocol was practical and acceptable. In order to confirm these results, and using the same study design, power estimates indicated that 260 children would need to be randomized.

Keywords: asthma, children, randomized control trial, inhaled corticosteroids, growth, bone, economics, quality of life.

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Introduction

Recurrent wheezing illness in childhood is a frequent reason for consultation in both primary and secondary care and whilst there is widespread support for the earlier introduction of inhaled corticosteroids (ICS) [1–3] concerns remain amongst parents and health care professionals about potential adverse systemic effects, particularly in growing children [4–6]. The benefits of their early introduction [7] and

increasing dose [8] have been questioned. As the majority of young children who present with wheezing remit spontaneously, the question remains who should be given ICS and at what stage of their illness [6]?

Explanatory trials generally measure the benefits a treatment produces under ideal conditions and have been used to establish the efficacy of the treatment. However, such trials rarely model real life, particularly in primary care where most patients are treated. What the primary care clinician requires are randomised studies within his/her environment in order to support rational choice. Randomized pragmatic trials were originally designed for settings in which placebo

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control is difficult or impossible to achieve. In contrast to explanatory trials, pragmatic trials aim to help clinicians decide between a new treatment and the best currently available. Pragmatic trials use a range of outcomes that reflect not only the clinical benefits but also the impact on the patient, cost effectiveness and possible adverse effects.

We conducted a pilot study using a randomized pragmatic controlled design in order to inform the planning and design of a definitive trial. The objectives of our pilot study were to establish likely recruitment rates, an appropriate protocol and to assess the short-term (6 months) outcomes of ICS treatment in order to refine sample size calculations for a definitive study.

Subjects and methods

Recruitment

Twelve primary care practices in North-East Scotland (Aberdeen City and Aberdeenshire) were approached and three urban and three mixed urban/rural practices agreed to participate. After Local Research Ethics Committee approval and agreement from participating primary care practitioners, potentially eligible children were identified from practice records. All were between 6 months and 16-years-old; had histories suggestive of asthma (at least two episodes of wheezing), which had commenced no longer than 12 months before, had not previously been prescribed prophylactic ICS and had no other known lung disease or concomitant illness. Episodes of wheezing were determined by physician's documented evidence (in the child's practice record), which were supported by evidence of treatment with β_2 -agonists.

Assessment

Children under the age of 6 years were assessed at the study centre (Royal Aberdeen Children's Hospital), while older children were assessed in their own primary care practices. At trial entry all children were already being treated with β_2 -agonist, in accordance with step 1 of the British Asthma Management Guidelines [1] and this continued irrespective of the trial allocation. Once written informed parental consent, and child's assent, had been obtained, children were randomly allocated, using a computerized stratification program, to either adding ICS (the experimental group) or continuing β_2 -agonists only (the control group). A process of minimization was used to ensure balance on: age, sex and primary care practice.

The aim of the pilot was to test a policy of early introduction of ICS as it would be used in practice. There was 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 [1]. The brand of ICS and choice of delivery device were left to the discretion of the primary care practitioner and practice asthma nurse. The doses recommended were within the ranges recommended in the appropriate data sheets and the British National Formulary, and were 200 μ g beclomethasone, budesonide, or 100 μ g fluticasone, all twice daily. 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 this was used on an as required basis only.

Children were assessed at entry and at 3 and 6 months. Once this was completed the primary care practitioner was advised to follow the British Asthma Management Guidelines [1].

Outcomes

Lung function

Forced expired volume in 1 s (FEV₁) was recorded using a 2120 hand-held storage spirometer (Vitalograph Ltd, Maid's Moreton House, Buckingham, UK) according to standard criteria. For those children too young to perform spirometry we assessed time to peak flow as a proportion of the total expiratory time ($T_{\text{ptef}}:T_e$) with respiratory inductance plethysmography [9]. Although the validity of this measure has been questioned it has been found to discriminate between normal and symptomatic populations and to demonstrate bronchodilator responsiveness [10].

Respiratory symptoms and health related quality of life

Subjective outcome variables for asthma treatment were assessed using a 31-day asthma diary, together with a standardized asthma questionnaire [11], Paediatric Asthma Caregiver's Quality of Life [12] and age-specific child administered quality of life questionnaires [13].

Growth and sexual maturation

Anthropometry was conducted according to standard procedures [14]. Body mass was measured to the nearest 100 g and sexual maturity visually assessed using the indices described by Tanner [14]. Girls were also asked whether menarche had occurred. Knemometry, a measure of knee to heel length, was assessed in children up to the age of 6 years using a modified hand-held trigger-activated portable device [15].

Bone mass and bone metabolism

Quantitative Ultrasound (QUS) examination of the left

os calcis was performed using a Contact Ultrasound Bone Analyser (CUBA) (McCue Ultrasonics Plc, Winchester, UK). Two indirect radiation free measures of bone mass were used: Broadband Ultrasound Attenuation (BUA) and Velocity of Sound (VOS) [16]. Evening spot urine samples were collected for collagen crosslink analysis. Pyridinoline (Pyr) and deoxypyridinoline (Dpd) are crosslinks in type I collagen which provide an estimate of bone resorption [17]. All urine samples were frozen and stored at -20°C until analysis. Pyridinoline and deoxypyridinoline were assayed by a fully automated technique using ion-pair reversed-phase high-pressure liquid chromatography on urine hydrolysates. Values were corrected for urinary creatinine concentration.

Economic issues

The costs of prescriptions were calculated using cost information from the 1997 British National Formulary and consultation costs approximated using the 1997 national estimates of £9 for a surgery visit, £27 for a home consultation, and £6 for a practice nurse consultation. Three measures of effectiveness were considered in the economic evaluation: symptom-free days; lung function measures; and health-related absenteeism from school.

Statistical analysis

All analyses used the intention to treat principle. Comparisons of continuous outcomes between treatment groups were performed using independent samples *t*-test or the Mann–Whitney test as appropriate. Comparisons of categorical data were performed using chi-squared *t*-tests. Comparisons between repeated measures were performed using paired samples *t*-test and Wilcoxon two-related-samples *Z*-test. Secondary analysis included analysis of covariance (ANCOVA) and logistic regression. Statistical significance was defined at the nominal 5% level.

Results

From the six primary care practices 15 036 children's records were reviewed, representing 18% of the total childhood population in Aberdeen City and Aberdeenshire (0–16 years of age). A total of 1617 (10.8%) had histories of recurrent cough/wheeze/asthma and were being prescribed β_2 -agonists as required. Of these 1617 children 1022 (63.2%) were already being prescribed an ICS. Of the remaining 595 symptomatic children 141 met the criterion of early asthma (<12 months duration). Of this eligible population 86 (57%) were recruited with 44 allocated to early ICS and 42 to continuation of β_2 -agonists alone, most (65, 76%) were under 6 years of age (Table 1). Fifty-five declined and 19 of these did so because of concerns about perceived side-effects of ICS.

The trial groups were similar at entry (Table 1), other than more in the experimental group came from households with a smoker. The preparations prescribed in the ICS group were beclomethasone ($n = 27$) and budesonide ($n = 17$); fluticasone was not prescribed. In the majority of cases ($n = 30$, 68%) the drug was delivered by spacer and metered dose inhaler; six (14%) used a dry powder inhaler; six (14%) a breath activated inhaler; and two (4%) a metered dose inhaler. Compliance was assessed in 40 of the 44 (91%) children randomized to ICS therapy. We were unable to assess compliance in four cases owing to lack of documented evidence of prescribed treatment in the child's primary care records. Compliance ranged from 25 to 150% (median 50%); 31 (77%) had a compliance of 50% or above and 16 (40%) 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. Ten children in the β_2 only group were later prescribed ICS (average 58 days from randomization, range 8–146 days) and four in the ICS group had ICS doses increased.

Seventy-nine children completed the study (40 and 39, respectively). Two withdrew because the family moved out

Table 1. Baseline characteristics of study groups

	ICS ($n = 44$)	β_2 only ($n = 42$)
Age, years [mean (SD)]	4.5 (3.2)	4.9 (3.1)
Male, n [%]	28 (64%)	23 (55%)
Height, cm [mean (SD)]	105.8 (20.2)	109.2 (19.6)
Weight, kg [mean (SD)]	18.5 (8.9)	20.4 (9.6)
One parent atopic, n [%]*	26 (59%)	31 (74%)
Sibling asthmatic, n [%]	18 (41%)	16 (38%)
Household with at least 1 smoker, n [%]	21 (47%)	10 (24%)

Inhaled corticosteroids and β_2 treatment (ICS); β_2 treatment alone (β_2 only). *Atopy defined as at least one of asthma, hayfever or eczema.

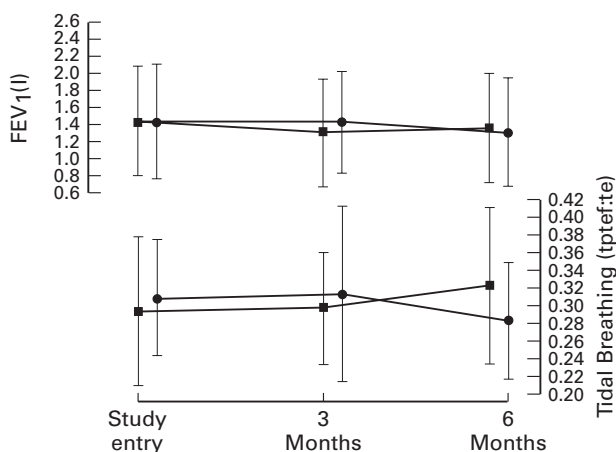


Fig. 1. Mean values ($\pm$ SD) for FEV₁ ($n = 38$) and tidal breathing parameters ($n = 55$) for ICS (●) and β_2 only (■) treatment groups.

of the area and the remainder because parents were unable to attend reassessment visits; there was no evidence that these children differed in any way from the other participants. No children had exacerbations requiring emergency consultations, hospital visits, or courses of oral steroids.

Lung function tests

FEV₁ and T_{ptef}:T_e were well matched at entry (Fig. 1). There were no significant differences between the groups at 3 and 6 months, although unlike the ICS group the β_2 only group's T_{ptef}:T_e had significantly increased from baseline at 6 months ($P = 0.044$). At 6 months the mean difference

between ICS and β_2 only for FEV₁ was -0.05 L (95% CI -0.41 L to 0.31 L) ($P > 0.05$). The mean difference between the groups for T_{ptef}:T_e at 6 months was -0.039 (95% CI -0.082 to 0.004) ($P > 0.05$). When baseline differences (age, household smoking) were incorporated into a general linear model (ANCOVA) no significant treatment group effects were found in FEV₁ at 6 months. However, the same analysis (ANCOVA) found a significant difference between T_{ptef}:T_e between treatment groups at 6 months ($P = 0.024$) in favour of the β_2 only group.

Respiratory symptoms and health-related quality of life

Respiratory symptoms and health-related quality of life were well matched at entry and respiratory symptoms improved over time in both groups (Table 2). When baseline measurements were incorporated as covariates in a logistic regression procedure the treatment group effect remained nonsignificant.

There were no significant differences between treatments in the caregivers' and children's quality of life scores at 6 months, apart from a lower child's quality of living score in the ICS group ($P = 0.013$) (Table 3). Significant improvement in caregivers' quality of life was observed ($P < 0.001$), but with the same improvement in both groups.

Growth and sexual maturation

No significant difference was found between the treatment groups with regard to stature at 6 months (Fig. 2), mean difference -3.6 cm (95% CI -12.6 cm to 5.4 cm). Although

Table 2. Health status and asthma diary record on entry and at 6 months by treatment group

	Study entry		6 months		Difference	95% CI
	ICS ($n = 44$)	β_2 only ($n = 42$)	ICS ($n = 40$)	β_2 only ($n = 39$)		
Episodes of wheeze > 4 events, n (%)	20 (46%)	19 (45%)	10 (25%)	7 (18%)	7%	-11% , 25%
Sleep disturbance due to wheeze > 1 per month, n (%)	11 (25%)	15 (36%)	4 (10%)	7 (18%)	-8%	-23% , 7%
Dry cough at night, n (%)	38 (86%)	35 (83%)	16 (40%)	18 (46%)	-6%	-28% , 16%
Sleep disturbance due to cough > 1 night per week, n (%)	21 (48%)	26 (62%)	16 (40%)	8 (21%)	19%	-0.3% , 39%
Wheezing limits child's speech, n (%)	9 (21%)	7 (17%)	3 (8%)	4 (10%)	-2%	-15% , 10%
Number symptom free days in 31 days, median (IQR)	—	—	27.5 (27, 31)	27.0 (13, 31)	0	-3 , 3
Total times reliever used in 31 days, median (IQR)	—	—	0 (0, 23.8)	5 (0, 19)	0	-5 , 0
Total symptom score in 31 days, median (IQR)	—	—	2.8 (0, 22.8)	3 (0, 11)	0	-3.5 , 1

Inhaled corticosteroids and β_2 treatment (ICS); β_2 treatment alone (β_2 only); interquartile range (IQR).

Table 3. Caregivers and child's quality of life on entry and at 6 months by treatment group

Caregiver	Study entry		6 months		Median difference	95% CI
	ICS (<i>n</i> = 43)	β_2 only (<i>n</i> = 42)	ICS (<i>n</i> = 40)	β_2 only (<i>n</i> = 39)		
Caregivers emotion score, median (IQR)	5.0 (4.0, 5.5)	5.1 (4.3, 6.0)	6.2 (5.6, 6.7)†	6.6 (5.6, 6.8)†	0	−0.34, 0.23
Caregivers activity score, median (IQR)	5.4 (4.4, 6.1)	5.5 (4.9, 6.1)	6.5 (5.3, 7.0)†	6.3 (5.5, 7.0)†	0	−0.5, 0.25
Caregivers total score, median (IQR)	5.2 (4.4, 5.8)	5.4 (4.7, 6.1)	6.1 (5.5, 6.8)	6.4 (5.3, 6.8)	−0.008	−0.41, 0.31
CHILD	(<i>n</i> = 20)	(<i>n</i> = 21)	(<i>n</i> = 17)	(<i>n</i> = 22)		
Child's Quality of living score, median (IQR)	31.0 (24.3, 30.5)	32.0 (28, 32)	30.0 (28, 34)	34 (26, 39)*	−2.25	−6, −1
Child's Distress score, median (IQR)	11 (7, 20)	7 (5, 21.5)	12 (18, 22)	5 (22.5, 49)	3	−1, 9
Child's Severity score, median (IQR)	10.0 (8.3, 13.8)	13 (11, 17)	10.0 (6, 12)	10.0 (8, 18)	0	−7, 4

Inhaled corticosteroids and β_2 treatment (ICS); β_2 treatment alone (β_2 only); interquartile range (IQR); *Mann–Whitney *U*-test, $P < 0.05$; †Wilcoxon two-related-samples *Z*-test, change from study entry, $P < 0.05$.

the mean difference between treatment groups for knee-heel length was -21.3 mm (95% CI -41.9 mm to -0.62 mm) at entry ($P = 0.044$) this difference disappeared after controlling for the slightly increased mean age of the β_2 only group (ANCOVA). At 3 and 6 months the mean differences for knee-heel length were -19.6 mm (95% CI -41 to 2.1) ($P > 0.05$) and -16.1 mm (95% CI -36.4 to 4.3) ($P > 0.05$), respectively. A secondary analysis of knee-heel length change, controlling for age (ANCOVA), indicated that age did not have

a significant effect ($P > 0.05$) and treatment effect remained nonsignificant at 3 and 6 months ($P > 0.05$). Knee-heel length and stature significantly increased over time in both groups ($P < 0.001$).

Height velocity over the six months was 0.13 (SD 0.08) cm/week for ICS compared to 0.15 (SD 0.04) cm/week for β_2 only (mean difference -0.015 cm/week, 95% CI -0.044 to 0.014) ($P > 0.05$). There was also no significant difference in knee-heel length velocity at 6 months 0.63 (SD 0.34) mm/week for ICS compared to 0.52 (SD 0.32) mm/week for β_2 only (mean difference 0.106 mm/week, 95% CI -0.070 to 0.282) ($P > 0.05$).

There were also no obvious differences in sexual development between the groups although the small numbers precluded statistical analysis. All the girls were premenarcheal with six having some signs of pubertal development, four in ICS group. Seven boys had signs of pubertal development, three in the ICS group

Bone mass and bone metabolism

Ultrasound of the os calcis was performed on 28 children over 6 years of age. No significant group differences for BUA was found on entry or at subsequent follow-up (Fig. 3), even after adjusting for age (ANCOVA). BUA between treatments at 6 months was 3.15 db/Mhz (95% CI -11.45 to 17.76) and for VOS was -7.8 m/s (95% CI -44.3 to 28.8), both nonsignificant.

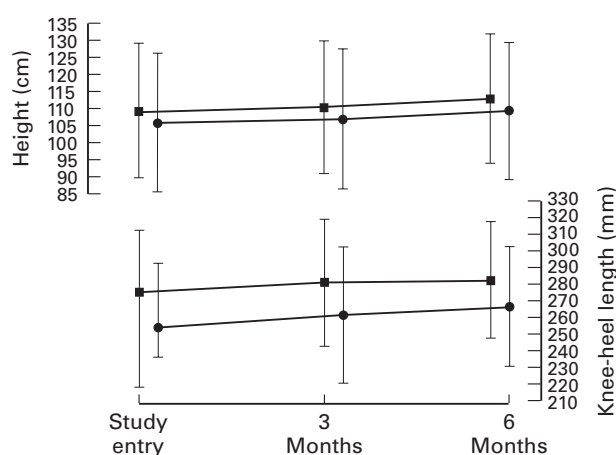


Fig. 2. Mean values ($\pm$ SD) for height ($n = 79$) and knee-heel length ($n = 57$) for ICS (●) and β_2 only (■) treatment groups.

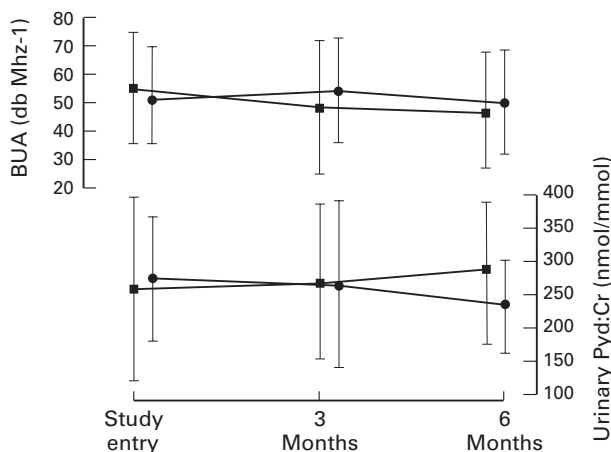


Fig. 3. Mean values ($\pm$ SD) for bone mass BUA ($n=28$) and urinary pyridinoline (Pyd) as a ratio of creatinine (cr) ($n=62$) for ICS (●) and β_2 only (■) treatment groups.

Urinary Pyd, normalized to urinary creatine, showed no significant differences at entry or at 3 months (Fig. 3). At 6 months the ICS group showed a reduction compared to the β_2 only who had increased their Pyd:Cr ratio ($P=0.028$), mean difference -52.2 nmol/mmol (95% CI -98.4 to -5.9). A secondary analysis (ANCOVA) adjusting for age confirmed the significant difference between treatments at 6 months ($P<0.05$). Urinary Dpd:Cr was also lower in the ICS group at 6 months, although the mean difference of -11.8 nmol/mmol (95% CI -28.3 to 4.66) was not significant ($P>0.05$).

Economic issues

Prescription costs were significantly higher for the children assigned to ICS with a mean additional cost per child of £20.73 over the 6 month period (95% CI 12.18 to 29.28). No significant differences were found for costs of both asthma-related and nonasthma-related primary care practitioner consultations and there were no hospital outpatient visits or inpatient stays recorded in either treatment group. When the 3 categories of health care cost were combined (surgery visit, home consultation and practice nurse) the mean additional costs per patient assigned to ICS was £17 (95% CI 3.2 to 30.7).

Discussion

The purpose of the study was to inform the design of a larger definitive study and a number of key issues emerged. Our recruitment experiences are salutary for future investigators attempting to study inhaled corticosteroids (ICS) treatment in young wheezy children. We found out of a total of 15 000 children and adolescents only 1% were eligible, of whom a third declined an invitation to participate.

The widespread and early use of ICS in symptomatic children seen in primary care could be explained by a number of factors. Asthma may be over diagnosed, guidelines may not be strictly adhered to in that ICS may be being used too early, or treatment options other than ICS may not be considered valid or appropriate for children.

The low drop out rate of those who were recruited 8% (7 of 86) provided evidence that the protocol was practical and acceptable. Our finding that more than 60% were aged 6 years or less was consistent with data from prospective cohort studies [18,19] suggesting that early intervention studies should focus on this young age group. However this produces another challenge in that approximately 60% of those presenting under the age of 2 years are likely to be asymptomatic by mid to late childhood [19].

Twenty-four percent of the control group (children randomized to β_2 alone) subsequently commenced ICS treatment, this was higher than the 9% of the experimental group (children randomized to ICS) whose ICS dosage increased. This suggested a significantly higher level of treatment failures in the β_2 only compared to the ICS group. However, none of the children had serious exacerbations as evidenced by the need for courses of oral steroids or hospital admissions. It was also not clear from the records available to us why these decisions to either start or increase ICS were made. Our analysis was by the intention to treat principle and in a definitive trial with larger numbers a sub analysis taking into account code violations would be possible while seeking to identify the reasons for commencing or increasing the dose of ICS.

The lack of evidence to support a substantial beneficial effect of early intervention reflected the inadequate power of the pilot study. Compliance is also an issue as 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 [20], short-term effects will obviously be confounded by the extent to which an individual takes their medication. However, the present study is similar to previous reports [21–23], which have found that even in closely regulated clinical trials only about 50% of inhaled medication is taken as prescribed. This suggests that we have observed real differences in treatment and not just the effect of poor compliance.

When deciding required sample size for a definitive study 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.

Asthmatic children using ICS have been shown to improve FEV₁ by approximately 9% [24]. 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 around 8 years. The mean FEV₁ for an 8-year-old

boy is $1.55 (\pm 0.199)$ [25]. Therefore, a long-term trial with 260 children would have 90% power to detect a 9% difference in FEV_1 at the 5% level [26].

Measures of FEV_1 have been shown to give a reliable reflection of lung function in children over the age of 6 years, but in younger children meaningful results have been difficult to obtain [27]. As indicated from the present study the majority of newly presenting ICS naive children are likely to be less than 6 years of age, and thus require other respiratory function assessments of short-term outcome. In the present study we assessed tidal breathing parameters using respiratory inductance plethysmography, recording the ratio of time taken to reach peak expiratory flow (T_{ptef}) to the total expiratory time (T_e). Although studies of $T_{ptef}:T_e$ in infants have shown associations with subsequent development of wheezing episodes [28], it has been suggested that in older children this ratio may be less sensitive to subtle deficits in airway function than spirometry [29]. The results presented here (Fig. 1) appear to confirm this conclusion, in that $T_{ptef}:T_e$ showed a large degree of variability and thus a lack of sensitivity. We suggest that measures of $T_{ptef}:T_e$ should not be included in subsequent trials, which include young children unable to perform spirometry, and that other measures, such as respiratory resistance using the interrupter technique [30], might be more appropriate.

Other important issues being addressed in the pilot were the possible adverse effects of ICS particularly on growth and bone development. We found a mean increase in stature of $3.38 (\pm 1.01)$ cm in the ICS group compared to $3.99 (\pm 1.25)$ 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 ($P < 0.05$) would require 130 children per group [26]. In a recent short-term study of prepubertal children (aged 7–9 years – albeit a more restricted age range than in the present 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 [31]. A trial size of 260 would have 90% power to identify a difference of 0.4 of a standard deviation (1 cm/year), and 80% power to identify a difference of 0.35 of a standard deviation (0.9 cm/year).

Measures of bone turnover (urinary pyridinium crosslinks, Pyd and Dpd) were lower than baseline in the ICS group whilst higher in the β_2 only group. This difference was significant for Pyd but not for Dpd, suggesting that collagen metabolism in tissues other than bone may also have been affected in the ICS group, since Pyd is known to have a somewhat wider tissue distribution than Dpd. These results are consistent with another study in children which found that bone formation and turnover decreased during

ICS treatment whilst linear growth was preserved [32]. Studies of urinary excretion of pyridinium crosslinks in healthy 4–10-year-olds indicate a similar trend to that found in our β_2 only group [33], whilst measures of collagen turnover have been found to be reduced in children receiving long-term ICS treatment [34]. Although studies of adults have shown an association between reduced bone mineral density (BMD) and inhaled steroid therapy [35], no effects have so far been observed in children [36], as in the present study. One possible interpretation is that ICS in moderate dosage may have their greatest effect on bone architecture rather than on bone mass or linear growth. Whether the observed changes in markers of bone turnover we observed were clinically important remains to be established. Our data indicate that a trial with 130 children in each group would have greater than 90% power ($P < 0.05$) to detect a 20% difference [26].

With respect to the four aims of the health economic component, since there was no evidence of greater short-term effectiveness in the early prophylaxis arm it was not possible to calculate a cost-effectiveness ratio. However, we did show that it was feasible to collect data retrospectively on use of Health service resources and prospectively on symptom free days and absenteeism via patient diaries. The data collected with respect to drug costs and consultations were then used as a basis for sample size calculations, however, the absence of inpatient admissions caused a problem as it would take very few inpatient admissions to dwarf the estimated difference in costs of prescriptions and unscheduled consultations. However, the outcome measures used would be suitable for making comparisons in terms of cost-effectiveness with other 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.

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 as the current study was not designed to establish the cost-effectiveness of early asthma prophylaxis. A major challenge in any future trial concerns the relationship of cost differences in the first six months following randomization to cost differences over an extended period of time.

Although our results showed no effects or detectable benefits of early ICS intervention the inadequate power of this pilot study make it impossible to determine the validity of these results. It is also possible that the failure to demonstrate any benefits may have been related to the short time period of the study, as a gradual response to ICS has been previously reported in adults. It could also be that in this young population with predominant mild disease early anti-inflammatory therapy may not be as effective as it

is in adulthood, as suggested by two recent explanatory trials [7,8].

Despite a greater awareness of the disease and improved treatment, asthma and wheezing illness presenting in childhood remains a major challenge. Although evidence for a more liberal use of ICS has been presented [37] our findings suggest that the widespread use of ICS in young children with symptoms suggestive of asthma merits review. In order to confirm these results, and using the same study design, power estimates indicated that 260 children would need to be randomised for a definitive trial. However, the short-term effects suggested in this pilot study, particularly with regard to bone turnover, emphasize the need to monitor the long-term risks, costs and benefits of early introduction of ICS, particularly in the young symptomatic child.

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