REVIEW

Evaluating the effects of asthma therapy on childhood growth: principles of study design

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Evaluating the effects of asthma therapy on childhood growth: principles of study design. J. Price, P. Hindmarsh, S. Hughes, J. Efthimiou. ©ERS Journals Ltd 2002.
ABSTRACT: Inhaled corticosteroids have been established as the most effective treatment for childhood asthma. However, concerns persist regarding their potential effects on growth and, most importantly, final height.

To assess their effects on growth, inhaled corticosteroids can be compared with placebo (type 1 study), nonsteroidal anti-asthma therapy (type 2 study), another inhaled corticosteroid (type 3 study) or "real-life" anti-asthma therapy (type 4 study). Owing to the difficulties in obtaining final height data, several different surrogate measures have often been used: short-term lower leg growth, longer-term statural height growth velocity, childhood height and predicted final height.

This paper discusses the choice of end point, key trial design issues (including selection and number of subjects in the active and control populations) duration of assessments and methods for measuring height and data analysis, in the context of the different study types.

Specific study design recommendations have been developed after consideration of these factors, and these principles will be used to guide the interpretation of previously published growth studies.
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The potent anti-inflammatory effects of corticosteroids rapidly established these agents as the most effective treatment for asthma. However, the systemic effects of oral corticosteroids were soon observed in children, who developed central obesity and reduced growth velocity [1, 2]. This led to the development of methods to deliver corticosteroids directly to the lungs by inhalation and the introduction of inhaled beclomethasone dipropionate in the early 1970s [3, 4]. Drug delivery by inhalation proved to be advantageous as the systemic effects typically associated with oral corticosteroids were reduced to a minimum [5]. Recent data have indicated the introduction of inhaled corticosteroids reduces asthma-associated growth suppression, by allowing reduced use of oral corticosteroids and improving the control of asthma [6]. In the development of treatment regimens to optimize the control of asthma symptoms, there has been a trend for progressively higher doses of inhaled corticosteroids to be used in milder asthma and in younger children.

Inhaled corticosteroids remain the most effective treatment for persistent asthma and are recommended as first-line therapy for children with persistent symptoms [7], although concerns persist regarding their possible effects on childhood growth and particularly effects on adult height. The interactions of glucocorticosteroids with growth hormone and the regulation of growth are complex. Acute exposure to glucocorticosteroids can enhance growth hormone release [8], but long-term exposure impairs its release [9]. Glucocorticosteroids can also inhibit the effects of growth hormone at target tissues and reduce the activity of insulin-like growth factor-1 [10]. The effect of systemic glucocorticosteroids on growth is thought to be dose-dependent [11]. Thus, all inhaled corticosteroids could, in theory, cause growth impairment if administered at a sufficiently high dose.

In July 1998 the Food and Drug Administration (FDA) held a 2-day meeting, reviewing all relevant inhaled and intranasal corticosteroid data with regard to childhood growth [12]. The stated aim was to consider making recommendations about class labelling for these treatments, to safeguard the health and safety of children with asthma requiring such treatment. Of the 55 studies reviewed by the FDA, most were considered to be poorly designed and generally the results of these latter studies showed no effect on growth, or were inconclusive. Only four randomized studies of at least 6 months' duration were considered well-designed [13–16], and these showed a mean reduction in growth velocity of 1 cm·yr^{-1} compared with placebo or other control (0.5–1.5 cm·yr^{-1}). These studies also showed a mean reduction in height velocity standard deviation score (SDS) of 0.58 (0.28–0.88).

On this basis the FDA recommended class labelling for all inhaled and intranasal corticosteroids pertaining to the possible effects on growth velocity in children with asthma [12]. They recommended that

growth should be regularly monitored by stadiometry in patients receiving these agents, that each patient should be titrated to the lowest effective dose, and that growth studies would be required for all new products and requested for all approved products.

The FDA also recommended the following "gold standard" for the design of growth studies: 1) a minimum of 6 months' run-in, with height measurements made on at least three separate occasions, 2) a minimum of 1 yr's randomized treatment to avoid seasonal effects and 3) a 6-month follow-up period at the end of the randomized phase, during which nonsteroidal treatment is administered. Clearly this latter recommendation poses substantial medical and ethical problems in patients whose asthma is wholly or partly controlled by inhaled steroids, as well as being impractical to conduct and fraught with difficulties in terms of analysis.

Careful consideration of many different factors is required when interpreting the data from growth studies, as several aspects of study design can confound the results. In addition, the fact that asthma itself can affect childhood growth further complicates the interpretation of these studies [17–19]. Long-term, accurate and precise measurement of growth is necessary to avoid the problems of short-term and seasonal variations in growth velocity. The inclusion of a valid comparator group is also important, while a relatively large number of patients is required to provide appropriate statistical power. In many studies, fixed-dose inhaled corticosteroid therapy is used and, consequently, children whose asthma symptoms are well controlled receive a higher dose than they would do in clinical practice. These and a number of other key issues necessitate careful consideration in designing and interpreting the results of growth studies in children with asthma.

The purpose of this two-part review is to highlight key factors to be considered when designing or appraising studies to assess the effect of inhaled corticosteroid treatment on growth velocity, and to examine the findings of previously published studies. The first part will focus on aspects of study design and provide recommendations for the design of scientifically robust growth studies. The second part will comprise a systematic review of published growth studies, and discuss the design and results of these studies in light of these recommendations [20].

Factors affecting childhood growth

Childhood growth is a complex process, dependent upon pulsatile, principally nocturnal, release of hormones (principally growth hormone) and, in later childhood, sex hormones [10]. Three distinct postnatal growth phases are identifiable. During infancy, there is a period of rapid growth, with body length typically increasing by 50% in 1 yr. The height achieved at the end of this growth phase is principally dictated by genetic and nutritional factors, but birth weight exerts an influence on growth velocity. Prematurely born infants, and some individuals who were small for their gestational age, demonstrate "catch-up" growth during the first year of life, and this process may continue for as long as 2 yrs. Following infancy, there is a period of gradually decelerating growth that lasts until puberty. During this period, growth is mostly determined by growth hormone secretion alone, and few children cross into different height percentiles. The third growth phase is associated with puberty and consists of an initial period of slow growth (slower than the previous years of relatively steady growth) followed by a growth spurt that lasts ∼2 yrs. Sex steroids and growth-hormone control this phase of growth. Importantly, many other factors can affect growth velocity during all phases of childhood growth (table 1), and these need to be accounted for when designing scientifically robust growth studies.

Growth study design classification

At the outset of a clinical trial, it is important to clarify whether the aim is to measure the absolute effect of an inhaled corticosteroid on growth or to compare it with an alternative treatment approach (e.g. alternative inhaled corticosteroid, or nonsteroidal therapy with or without oral corticosteroid treatment as required). The present authors have devised a simple classification system for clinical trials assessing growth in children with asthma receiving inhaled corticosteroids (fig. 1). Type 1 studies use a placebo group for comparison with inhaled corticosteroid treatment; type 2 studies use nonsteroidal asthma therapy as the comparator; and type 3 studies compare one inhaled corticosteroid with another. Type 4 studies are "real life", typically observational

Table 1. – Potential confounding factors in studies evaluating the effects of asthma therapy on childhood growth

Psychosocial deprivation	Socioeconomic status	Congenital disease (e.g. Klinefelter's syndrome, Turner's syndrome, growth hormone deficiency)
Age	Seasonal variations in growth (annual)	
Puberty		Age of onset of wheezing
Sex	Long-term oscillations in growth (e.g. mid-childhood growth spurt)	Severity of asthma symptoms
Ethnicity		Well-controlled asthma has less effect on growth than poorly controlled asthma;
Parental height		
Circadian variations (daily)	Administration of systemic corticosteroids for asthma or other diseases	
Compliance with corticosteroid medication		Systemic absorption of inhaled corticosteroids is reduced among patients with severe asthma
Exposure to tobacco smoke	Administration of topical corticosteroids for eczema or allergic rhinitis	
Nutrition		Other chronic disease (e.g. inflammatory bowel disease, chronic renal disease, coeliac disease)
Birth weight (affects growth during infancy)		

	Type 1	Type 2	Type 3	Type 4 "real life"
Comparator	Placebo	Nonsteroidal asthma treatment	Inhaled corticosteroids	Normal asthma treatment
Design	Prospective, randomized, controlled studies			Prospective, retrospective or observational studies
Primary end point	Growth velocity			Final adult height or growth velocity

All growth studies

Key principles

≥ 12 months duration
Stadiometry/trained investigator
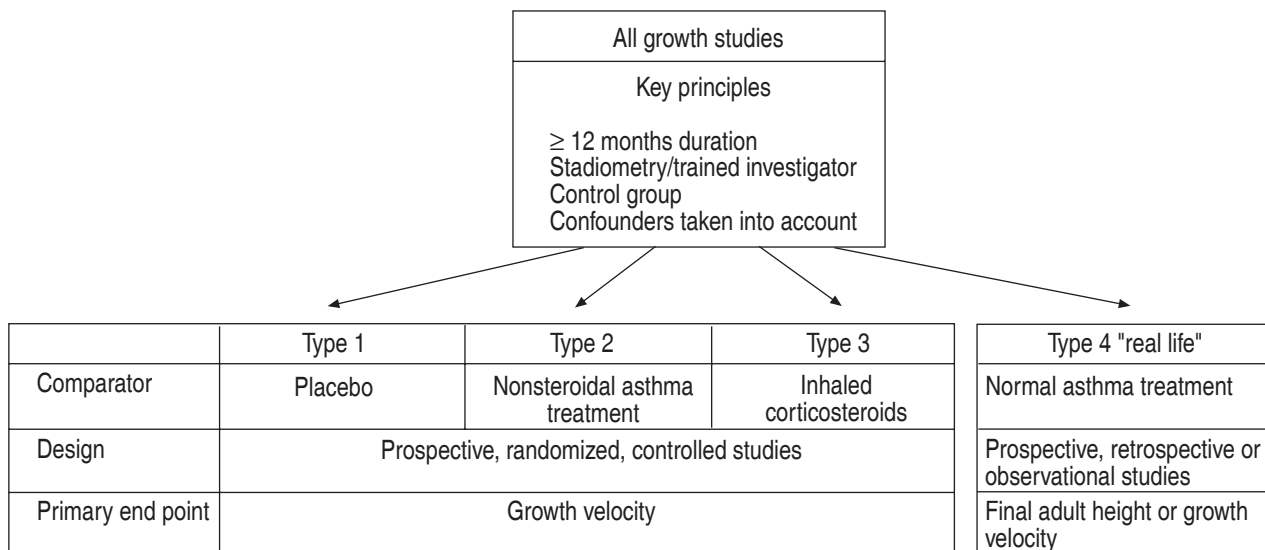Control group
Confounders taken into account

Fig. 1. – Classification of growth studies in children with asthma.

studies, and the inhaled corticosteroid is compared with any other treatment the patient requires and the dose is adjusted according to asthma control, as is normal in clinical practice (usually the dose of inhaled corticosteroid is also adjustable). Study types 1–3 are randomized prospective studies and provide direct controlled comparison between treatment groups in the clinical trial setting. However, type 4 studies may not be randomized, and may not be prospective (*i.e.* specific patients may be followed from the beginning to the end of the study, or data on a group of patients may be collected retrospectively using treatment databases). The "trunk" criteria or minimum requirements for all these studies are: statural height measured by stadiometry and a minimum study duration of 1 yr. Stadiometry is widely acknowledged as the most reliable means of measuring height, while a study period of 1 yr is long enough to avoid potentially confounding seasonal variation in growth, and to establish the presence of a genuine treatment effect.

A type 1 study may provide ideal data for measuring the absolute effect of the inhaled corticosteroid on growth, indeed, the FDA have recommended this type of study be used for this purpose. However, there are both ethical and statistical problems associated with this approach. Ethically, type 1 studies are only feasible in patient populations with mild-to-moderate asthma, as placebo is inappropriate for patients with more serious disease, prone for example to significant symptomatic deterioration and exacerbations, and ethical recommendations are continuing to tighten in many countries. As a result, it is not possible to directly compare high-dose inhaled corticosteroid treatment with placebo in an appropriate patient population. In addition, withdrawal of patients experiencing severe symptoms of asthma is significantly more likely from the placebo group, leading to an imbalance in disease severity in the two groups completing the trial. Since disease severity can affect growth velocity (discussed further in the Selection of subjects section) [11, 19] a bias towards

greater growth velocity in the placebo group can be expected. An additional source of bias could be improved asthma symptom control in the inhaled corticosteroid group compared with the placebo group, although the effect of this on growth velocity remains to be determined.

Nonsteroidal therapies are considered to have no direct effect on growth velocity and the ethical difficulties with this type of study (type 2) are reduced in comparison with the inclusion of a placebo group. However, differential symptom control with steroidal *versus* nonsteroidal therapy could bias the results in the same way as for type 1 studies, and to minimize the likely differences type 2 studies are only suitable for patients with mild-to-moderate asthma. Since oral corticosteroids may be required to control exacerbations, particularly for patients with less mild disease, type 2 studies will likely compare the inhaled corticosteroid with an alternative "treatment strategy" as opposed to strictly nonsteroidal therapy. Clearly, all oral corticosteroid use needs to be carefully documented. Another disadvantage of a study comparing an inhaled corticosteroid with nonsteroidal treatment is that blinding can be difficult. Nevertheless, there are medical and ethical arguments in favour of type 2 studies over type 1, as all patients receive some form of anti-inflammatory treatment. Statistically, both type 1 and type 2 studies should be designed to establish at least noninferior growth in the inhaled corticosteroid group (*i.e.* one-way equivalence studies).

Type 3 studies are useful in enabling physicians to choose between different inhaled corticosteroids for the treatment of children with asthma. A distinct advantage of these studies is that patients with more severe asthma can be enrolled with a minimum of problems from differential symptom control in the two study groups. Type 3 studies cannot, however, provide information on the absolute effect of a particular inhaled corticosteroid on growth. Also, the use of oral corticosteroids by patients in type 3 studies

will complicate the interpretation of the results, as any reduction in growth could be attributed to either form of corticosteroid therapy. Statistically, type 3 studies may be powered to establish noninferiority or superiority depending on whether the objective is to show that the inhaled corticosteroid is as good as or better than the comparator in terms of any effect on growth velocity (discussed in Data analysis section).

A weakness of study types 1–3 is their use of fixed-dose medication. This is impractical in the long-term and inevitably leads to some patients receiving inappropriate doses, in the case of inhaled corticosteroids this may lead to unnecessary systemic effects and therefore, potentially, reduced growth velocity. By allowing appropriate dose adjustment, type 4 studies are more likely to give a true indication of effects on growth velocity as seen in clinical practice. Also, because a variety of comparator treatments can be used, there is little constraint on the severity of asthma that can be assessed in type 4 studies. This is the most suitable study type for assessing treatment effects on final height. However, a delay of puberty caused by inhaled corticosteroid treatment may not be detected if final height is the end point; height measurement throughout the study is necessary to fully characterize any treatment effects on growth. One of the main difficulties with type 4 studies is statistical analysis. Events that could affect growth such as dose adjustment, use of oral corticosteroids and poor asthma control will occur in most subjects during long-term studies, and it may be expected that not all these events will be fully documented. In addition, if the study is retrospective, differing prescribing practices may have resulted in only the more severely ill patients receiving inhaled corticosteroids and hence again disease and drug effects are confounded. Type 4 studies showing similar outcomes between treatment groups indicate that the inhaled corticosteroid does not impair growth, but if there is a difference between patient groups the difference may not be able to be attributed to the study treatment. Thus, type 4 studies should always be designed to establish noninferiority as opposed to superiority.

A further consideration regarding type-4 studies relates to generally accepted treatment guidelines which include "step-down" therapy for individuals whose asthma has been brought under control. This approach can be adopted to ensure that the study reflects everyday clinical practice, although care must be taken to avoid exacerbations caused by premature or excessive dose reductions. The starting dose may either be fixed for all subjects, or chosen by the investigator according to each patient′s requirements.

Growth studies: design criteria

Choosing a parameter to assess effects on growth

It is important that a suitable parameter is chosen to measure the effects of an inhaled corticosteroid on growth. In the long-term, final height is of most interest to physicians, patients and their parents. However, the difficulties of obtaining final height data dictate that suitable surrogate parameters are used. The principal end points that have been used in previous studies will now be reviewed.

Lower leg growth during childhood. Knemometry is a sensitive technique used to measure short-term changes in lower leg length. The accuracy and precision of knemometry measurements are usually high. However, knemometry data correlate poorly with statural height and tend to overestimate any potential effects on growth [21, 22]. The technique is confounded by movement of dermal water in the lower leg, reducing the accuracy of measurements and questioning the relevance of this parameter as a true growth measurement [23]. In addition, short-term measurement of growth is prone to poor reproducibility due to seasonal variations. Thus, short-term lower leg growth is subject to misinterpretation if an attempt is made to relate the data to long-term statural growth.

Growth during childhood. There is no clear relationship between growth velocity during childhood and final height [24]. However, given the difficulties of obtaining final-height data and the lack of sensitivity when measuring height, growth velocity during childhood is an attractive option for assessing the effects of inhaled corticosteroids for study types 1–3 (and for short-duration type 4 studies). Assessments of growth velocity must account for all of the key sources of variability in growth (table 1), and the choice of an appropriate comparator group is of importance.

Successive measurements of growth velocity are not well correlated because of the cyclical nature of growth over the short (1-yr) and longer term (2-yrs) [25, 26]. Given the cyclical nature of growth, control data are essential for any study and, because of the longer-term trends in childhood growth (fig. 2), it would be unwise to incorporate a wide range of ages into any particular study. A wide age range implies a wide range of expected growth rates, increasing the difficulty of detecting treatment effects.
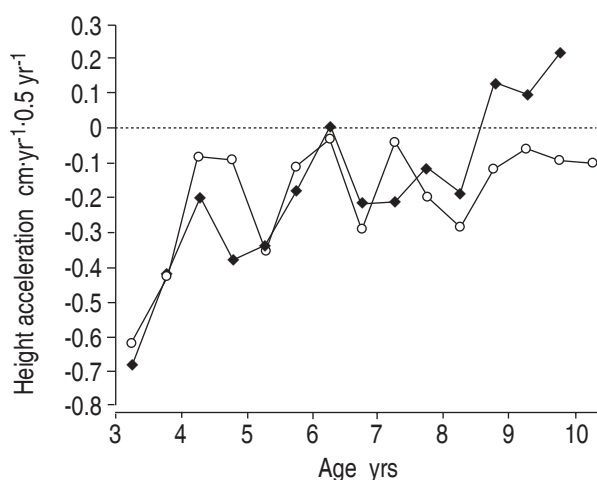

Fig. 2.–Cyclical patterns in childhood growth. Reproduced with permission from [26]. ○: males; ◆: females.

A number of different methods can, in theory, be used to assess childhood growth. Extrapolation of knemometry data to longer-term childhood growth (*e.g.* annualizing 1-month data) has limited value because of short-term variability in growth velocity [22, 27]. Furthermore, if an inhaled corticosteroid affects growth to a certain extent during the early months of treatment, with growth velocity during later treatment approaching normal (as suggested in some studies) [16, 28] annualizing short-term data would overestimate the effect of treatment on growth. Change in height from the beginning to the end of a long-term study can be used, but the use of just two time points considerably increases the potential for inaccurate data due to measurement error. A more accurate estimate of growth rate is obtained by measuring height at a number of time points during the study, then performing linear regression of height against time. Growth velocity data are therefore dependent on the precision and accuracy of height measurement, upon which is superimposed the biological variability arising from short- and long-term growth cycles.

Comparison with normal growth values from a population of healthy children is possible, and is one method favoured by regulatory authorities and growth experts, not least because the method allows correction for any intergroup differences in age or sex distribution. To achieve this, data from the study population are converted to growth SDS. This involves subtracting the "standard" or normal growth velocity for the subject′s age and sex from the observed value in the population, and dividing the result by the standard deviation of the standard population value. The sole focus in this case should be comparison between study groups rather than comparison with a "normal" population, as differences from "normal" values could either be due to asthma itself or to the treatment. For patients with severe disease, who require high-dose inhaled corticosteroid therapy, reduced growth velocity is likely to be observed but cannot simply be interpreted as being due to the corticosteroid. Also, the effect may not be unacceptable in this population, because poorly controlled asthma may lead not only to impaired growth, but also to serious morbidity or even death. SDS may also be helpful in determining the effect of asthma itself when examining differences in growth velocity between asthmatic patients treated with placebo or nonsteroidal anti-inflammatory agents and age- and sex-matched healthy subjects. This is most likely to be applicable in type 1 and 2 studies. "Normal" population data are unavailable for most national populations, making it impossible to account for ethnic or environmental differences that are particularly problematic in multicentre studies. Whatever method is chosen to measure growth, it is important to consider the limitations of all growth velocity data, given the potential variability of growth velocity over time for any individual child.

Height during childhood. Unlike growth velocity, measurement of height at a particular age correlates well with final height [24, 29]. This is not surprising

as, although height is dictated by cumulative growth rate, the correlation relates to the probability of an individual remaining within the same height percentile after a period of time. Successive height measurements are highly correlated, particularly in prepubertal children after the age of 3 yrs, as these children generally remain in the same height percentile until the onset of puberty. Prior to this age, height adjustment from infant levels to the genetically determined percentile causes considerable variability. Height does not provide a sensitive measure of impaired growth for the whole study population, as a reduction in growth velocity may not be manifested as a noticeably low absolute height at the end of a study period. Therefore, height alone is a less suitable parameter than growth velocity for the primary end point in study types 1–3, and short-duration type 4 studies. However, it can be helpful in assessing individual patients whose growth, and therefore longer-term height, is severely affected by steroidal treatment.

If height is to be used as a study parameter, height at the beginning and end of treatment should be expressed in height centiles with respect to the "normal" population and compared. A shift to a lower centile over the period of the study can be interpreted as evidence of impaired growth.

As mentioned earlier, the use of just two time points increases the potential for inaccurate data due to measurement error. Therefore, the accuracy and precision of height measurements made by trained staff using high-quality apparatus becomes even more important.

Predicted adult height. A number of different methods have been used to predict children′s final height. The most commonly used are those of Roche, Waine and Thissen [30], Bayley and Pinneau [31] and Tanner and Whitehouse [32], all three of which require assessment of skeletal maturity [30–32]. The 95% confidence intervals of these methods are ∼7–9 cm in healthy individuals [33]. The accuracy of the Tanner–Whitehouse technique [32] has been optimized by including allowance for parental height as well as height and skeletal maturity. Height alone may be used to predict final height. For healthy children, the 95% predicted interval for final height has been shown to be ±1.5 SDS (*i.e.* ∼10 cm) around the value that was predicted using height alone [29]. As with the Tanner and Whitehouse method, the inclusion of midparental height improves the estimate predicted final height.

As with height, it is questionable whether corticosteroid treatment would exert a measurable or clinically significant effect on predicted adult height during a study period, particularly if there is a lag between the treatment and an effect on skeletal ossification. Measurement of the effect of inhaled corticosteroids on predicted final height will be complicated by the fact that asthma itself can delay skeletal maturity and affect childhood growth patterns. In addition, bone age can only be estimated accurately in children aged >2 yrs, and height prediction is only reliably performed in children aged >6 yrs. Therefore, predicted final height is not

considered as a suitable primary end point for study types 1–3 and short-duration type 4 studies.

Final height. Reduced final adult height is the principal clinical concern and is the preferred primary end point for type 4 studies, but it is the most difficult end point for obtaining prospective data. Measurements of final height have similar accuracy and precision to measurements of height during childhood, but the long duration of final-height studies means that such data cannot be obtained until the drug has been available for many years. Prospective, randomized, double-blind studies are impractical and very expensive, and complete datasets (including total corticosteroid use, disease control and severity) are difficult to obtain from retrospective studies. Nevertheless, one large, long-term prospective study has now been performed in children with complete datasets [24]. This showed that treatment of asthma with budesonide had no effect on final height, despite a significant decrease in growth velocity during the first 2 yrs of treatment.

It is possible to include additional factors to improve the interpretation of data when using final height as the end point. The spread of heights in the general population is ∼23 cm; this can be reduced to ∼8 cm if parental height is used and to 4 cm if predicted height is used (the spread of predicted height is dependent on the age at which the estimate is made: approximate values are 7 cm at 6–11 yrs, 5 cm at 12 yrs and 4 cm at 13 yrs) [32]. These reductions in error facilitate detection of an effect of corticosteroid therapy on final height by increasing the accuracy of the expected outcome (*i.e.* if future growth remained unaffected). It is therefore recommended that final height is predicted at the outset of all final height studies, even when a nonsteroidal control group is included, to maximize the likelihood of detecting a treatment effect. In addition, if parental height is to be used, the same rigorous measurement guidelines as applied to patient measurements should be applied.

Selection of subjects

Age/pubertal status. Growth during puberty is highly variable, usually nonlinear and difficult to predict. Therefore, to avoid this problem and obtain a sensitive measure of drug effect, it is necessary for studies measuring growth velocity, change in height or change in predicted final height to include only prepubertal children [34]. Upper age limits should be implemented in these studies to ensure that the subjects' growth is not affected by puberty or prepubertal growth deceleration during the study; these are 9 yrs for females and 9.5 yrs for males. Additionally, sexual maturity should be assessed to ensure prepubertal status, the Tanner sexual maturity rating scale is commonly used to achieve this (a rating of >1 is generally interpreted as onset of puberty) [35]. It is necessary to assess sexual maturity not only at the outset of the study, but also at the end of the study period to ensure that puberty does not affect growth measurements taken during the study. It is advisable

to avoid the inclusion of patients with a large age range, as this would create the potential for increased intersubject variability, due to the cyclical nature of childhood growth and altered accuracy in height prediction [26].

For studies of final height (usually type 4), it is preferable to recruit children who are initially prepubertal, to ensure that the effects of treatment throughout childhood are assessed. Clearly, children entering puberty during the study are not excluded.

A lower age limit of 4 yrs is generally appropriate for all study types because of the changing influences of hormonal and nutritional factors on growth velocity in younger children, and the lower age limit is raised to 6 yrs if predicted adult height is one of the study parameters. However, in some circumstances it is necessary to assess the effect of inhaled corticosteroid therapy in younger children. Children younger than 4 yrs should in all cases be studied separately, and care must be taken to account for factors such as birth weight and nutrition. Standing stadiometry is only possible for children who are older than 1 yr, though infants' length can be measured accurately and precisely using an infantometer, which measures the length of the infant lying down.

Severity of asthma/asthma control. To minimize intersubject variability, it is necessary to recruit children with as narrow a range of asthma severity as possible. The choice of asthma severity depends on the type of study performed. As mentioned earlier, only populations with mild-to-moderate asthma are suitable for type 1 studies. For type 2 studies, mild-to-moderate asthma is also the least likely to present practical difficulties, as it is generally acceptable to treat this population with nonsteroidal therapy, and the variation between treatment groups in drop-out rates due to poor efficacy should be smaller. Only type 3 and 4 studies can include patients with higher disease severity, as all study participants may receive effective therapy for asthma. However, children whose disease is too severe to be controlled by inhaled corticosteroids alone are best excluded. These children are likely to receive oral as well as inhaled corticosteroids, which would preclude measurement of the absolute effect of the inhaled corticosteroid. The present authors recommend that no more than four courses of oral corticosteroids are permissible per year in growth studies, as children who receive more than this have demonstrated persistently reduced cortisol responses to adrenocorticotropic hormone [36].

Aside from the increased requirement for oral corticosteroid treatment, possible reasons for asthma causing growth impairment are: delayed puberty, reduced growth hormone secretion, other endocrine malfunction, decreased appetite and increased energy demands [11, 19]. Additionally, exercise may have a contributory effect, as children with asthma tend to exercise less than those without disease and exercise is associated with increased growth hormone levels in asthmatic children [37]. In any case, there appears to be a positive correlation between asthma severity and the degree of growth impairment [11, 19]. It is also worth noting that the systemic bioavailability

of inhaled corticosteroids is affected by disease severity. In healthy volunteers, pulmonary absorption of inhaled corticosteroids is higher than in patients with asthma, leading to greater systemic bioavailability [38]. Indeed, the evidence indicates that the greater the level of airflow obstruction, the lower the systemic exposure [39]. Therefore, to provide data that are relevant to clinical practice, the effects of high-dose inhaled corticosteroids need to be assessed in patients with appropriately severe asthma. Since type 1 and type 2 studies can only be performed in patients with mild-to-moderate asthma, high doses of inhaled corticosteroids cannot be compared directly with placebo or nonsteroidal therapy.

Besides disease severity, the degree of asthma control may also influence both the treatments required by the patients and their growth. Clearly these two are linked, but some patients may have mild-to-moderate disease which is not well controlled resulting in symptoms and exacerbations, while patients with more severe diseases may be well controlled on inhaled corticosteroids. The degree of disease control may, in such circumstances, have as substantial an impact on growth as the underlying disease severity. Ideally, both disease control and disease severity need to be accounted for throughout the study, to ensure that these factors do not affect growth independently of the study treatments.

Height and growth velocity. Children who are exceptionally tall, short, underweight or overweight may inherently have a growth velocity that is different from "standard" values [40, 41]. Thus, only children with height measurements within the percentile range 5–95% of normal values for their age should be included in all types of growth study. Nevertheless, it is worth noting that this precludes children who are already of short stature, in whom any impairment of growth would be of greatest concern. Separate studies in children at the lower end of the normal height range would therefore be desirable.

Patients should also be excluded if they are outside the normal range for growth velocity. For example, Turner's syndrome is associated with reduced growth, which would confound the effects of asthma or therapy on growth. The 10–90% percentile range for growth velocity seems to be appropriate for inclusion in clinical trials, but there are currently few data on which to base this conclusion. Selection of patients according to their growth velocity requires a run-in period of at least 12 months, to ensure accurate assessment of growth velocity. Assessment during run-in also enables comparison of growth velocity before and after inhaled corticosteroid treatment. However, such run-in periods pose substantial practical, medical and ethical challenges, particularly if treatment with inhaled corticosteroids is not permitted during this period.

Congenital and environmental factors. Patients with active or historical evidence of endocrine disorders (*e.g.* growth-hormone deficiency or thyroid-hormone deficiency or excess) should be excluded from all types of growth study. Other exclusion criteria include growth disorders (*e.g.* Turners' syndrome, Klinefelter's syndrome) and systemic diseases likely to affect growth (*e.g.* inflammatory bowel disease, coeliac disease, chronic renal failure). Exposure to cigarette smoke is not necessarily an exclusion factor, but should be recorded for inclusion in the data analysis, as should age of onset of wheezing.

Control population

The control and study populations should be well matched in terms of age, sex, pubertal status, height, growth rate (perhaps using a run-in period for assessment), and asthma severity and disease control at baseline. Other factors that may influence growth rate also need to be recorded at baseline (*e.g.* age of onset of asthma, socioeconomic status, exposure to tobacco smoke). Any differences between the populations can then be accounted for in the analysis of study results.

Differences between delivery devices used by the inhaled corticosteroid and control groups should be minimized, as the dose delivered to the patient's airways and particle size distribution vary between devices, potentially affecting systemic availability [42]. This consideration is most important for type 3 studies, as a true comparison of different inhaled corticosteroids can only be achieved if the delivery device is identical for the two drugs. In practice, this is not always possible, and use of the same type of device (*e.g.* dry powder inhaler, metered-dose inhaler) is the best compromise. Nevertheless, it is known that differences exist between inhalers of the same type from different manufacturers, and this should be borne in mind when interpreting the results [43].

Duration of growth assessment

As growth velocity varies over time, an extended period between the first and last height measurements is required to avoid short-term inaccuracies. One year is recommended as the minimum duration for study types 1–3, as this will prevent seasonal variation from affecting the results. The necessity for measuring height over at least 1 yr has been illustrated by a previous study, where estimates for annual growth velocity were derived from height measurements at 0 and 3, 6, 9, and 12 months. These estimates were then compared with the annual growth velocity measured by linear regression of height measurements taken every 6 weeks (fig. 3) [44]. For type 4 studies a minimum period of inhaled corticosteroid therapy needs to be considered. At least 1 yr may be appropriate, but there are few data to guide this decision and to some extent the decision will be guided by the objective and primary measure of the study (as in type 1–3 studies, age and pubertal status of the subjects may be critical).

Run-in and follow-up periods of 6 months' duration have been recommended by the FDA to allow growth measurements to be made in the absence of inhaled corticosteroid therapy. This would allow
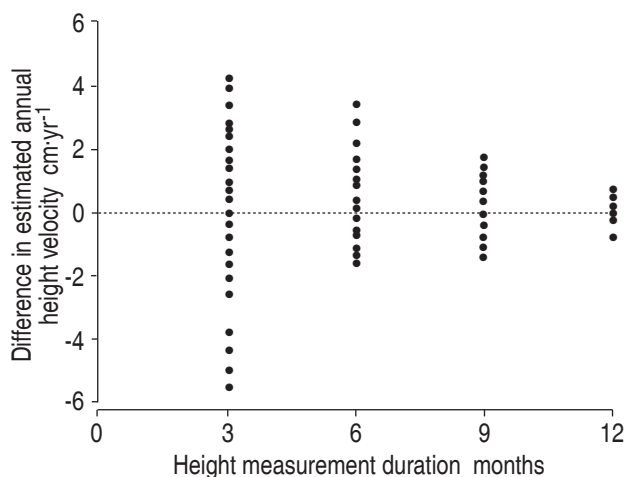
Fig. 3. – Differences in estimated annual growth velocity between two-point analyses based on different durations of height measurement compared with the estimate from 1 yr regression analysis [44].

growth velocity to be measured before treatment and for any catch-up growth after treatment cessation to be detected, improving the possibility of detecting any effect of the inhaled corticosteroid on growth. Ideally, the duration of the run-in and follow-up periods should be 1 yr to avoid the confounding short-term factors described earlier. However, there are likely to be substantial medical, ethical and practical difficulties with therapy during run-in or follow-up. In some countries, treatment of asthmatic patients with placebo or nonsteroidal therapy may contradict national guidelines on asthma therapy. An additional problem arises from patients withdrawing from the study due to poor disease control during run-in. This may bias the study population towards patients with more mild asthma, perhaps excluding a subset of patients who may be more or less sensitive to the effects of inhaled corticosteroids on growth. A follow-up period with discontinuation of corticosteroid therapy is ethically difficult to justify, and any variability of treatment and disease control during this period would make the results very difficult to interpret.

Measurement of height

A statement on height quality control assurance is essential in all studies. The optimal method for measuring statural height to assess long-term growth is stadiometry, assuming the subject is at least 2 yrs of age. Each participant should be assigned to a particular nurse for height measurement at every visit, to minimize any scope for interindividual variation [45, 46]. In one study, the coefficient of variation when the height of 22 individuals was measured by one observer (individuals measured five times) was 0.09, compared with 0.16 when individuals were measured by five different observers [44]. Other measures to ensure consistency include using standardized equipment, measuring height at the same time of day at each visit (to avoid potential variability from height

decrease during the course of the day) [45], and development of a protocol for height measurements. The written protocol should include details such as the necessity of wearing hair down, ensuring that subjects have bare feet and that body stature is consistent (e.g. unstretched chin level) [45, 46]. Height measurements should be made in triplicate, ideally with blinding to remove any bias associated with previous values, and the mean of the three values used for subsequent analysis [47]. Modern, digital stadiometers are capable of measuring height to the nearest 0.1 cm.

Measurements should be taken approximately every 3 months to optimize the accuracy of growth assessment. If it is desired to assess whether the effect of corticosteroid treatment on growth occurs only in the first few weeks of treatment, more frequent measurements should be taken at the beginning of the study.

Young infants' statural height, up to the age of 1 yr, is measured in the supine position using an infantometer or kiddimeter. As with stadiometers, digital apparatus is available to measure infants' length with an accuracy of 0.1 cm. However, the use of this apparatus introduces another complication due to an increase in measured height of up to 1 cm compared with using a stadiometer [48].

In general, methods of measuring statural height other than stadiometry or infantometry have not been standardized and are less reliable, although a recently developed portable apparatus using ultrasound to measure statural height has been shown to have accuracy approaching that of stadiometry [49].

Data analysis

Growth velocity. To determine the number of study participants required to power the study adequately, it is first necessary to identify the minimum inter-group difference that needs to be detectable (*i.e.* minimum detectable difference). This is determined initially depending on whether the study is seeking to establish noninferiority or superiority. Growth studies are distinct from efficacy studies in that noninferiority is sought in placebo-controlled trials (*i.e.* study types 1 and 2); superiority is sought only in studies comparing one inhaled corticosteroid with another. In the present authors' opinion, based on clinical practice and evidence from previous studies [34, 50], an inter-group difference of 0.8 cm·yr^{-1} should be detectable to establish superiority (type 3 studies). When studying efficacy, half the treatment effect is generally used to define the range for equivalence [51]. This suggests that the minimum detectable difference for noninferiority growth-velocity studies (*i.e.* study types 1, 2 and noninferiority type 3 studies) should be ±0.4 cm·yr^{-1}. However, the validity of applying principles used for efficacy studies to the context of safety studies is not known. Table 2 provides an indication of the patient numbers required to deduce noninferiority or superiority for a range of minimum detectable differences in growth velocity for each study type, with 90% power and based on a standard deviation of ≤1.4 cm·yr^{-1} [34, 50]. It should be noted that the

Table 2. – Patient numbers required to detect between-group differences in growth velocity (cm·yr^{-1}) for different types of growth study

Study type[#]	Study objective	Minimum detectable between-group difference cm·yr^{-1}	Minimum number of patients per treatment group[¶]
1	Non-inferiority	0.3	458
1	Non-inferiority	0.4	258
1	Non-inferiority	0.5	165
2	Non-inferiority	0.3	458
2	Non-inferiority	0.4	258
2	Non-inferiority	0.5	165
3	Superiority	0.6	115
3	Superiority	0.8	65
3	Superiority	1.0	42
3	Non-inferiority	0.3	458
3	Non-inferiority	0.4	258
3	Non-inferiority	0.5	165

[#]: See figure 1 for growth study design classification (*i.e.* types 1–4); [¶]: based on 90% power, 5% significance level and standard deviation of $\leqslant 1.4$ cm·yr^{-1} [34, 50].

numbers in table 2 are a guide only, and patient numbers would increase if the data were expected to be more variable. For example, if the standard deviation were 2.8 cm·yr^{-1}, the patient numbers would quadruple (*e.g.* 1,029 patients per group needed to establish noninferiority with a minimum detectable difference of 0.4 cm·yr^{-1} for study types 1 and 2).

For studies using growth velocity expressed in SDS as the primary end point, the sample size may be expected to be slightly smaller than for cm·yr^{-1}, as SDS accounts for variation due to age and sex. The present authors calculated SDS ranges for males aged 3 and 10 yrs corresponding to the minimum detectable differences used previously (cm·yr^{-1}), and assumed the middle of this range could be taken as the minimum detectable difference (SDS) for most studies. Table 3 provides an indication of the patient numbers required to detect a range of intergroup differences in growth velocity (SDS) for each study type, with 90% power and based on a standard deviation of $\leqslant 1.5$ SDS [34, 50]. Unexpectedly, the variability from these two studies (and therefore sample-size estimates) increased when using growth velocity SDS as opposed to growth velocity in cm·yr^{-1}. This is likely due to the fact that the standard charts, from which SDS are derived, are based on healthy children rather than children with asthma, and hence may not accurately reflect the population being studied.

Patient numbers are not included in the sample size tables for type 4 studies using growth velocity as the primary end point because there are insufficient data from studies of this type to estimate the variability reliably.

Comparison of the inhaled corticosteroid group with the control group is generally the main focus of data analysis, regardless of the study type. Conversion of height data to growth velocity (cm·yr^{-1}) can be done quite simply by constructing a regression slope for each patient using all height measurements taken at baseline and during the treatment period. The estimate of growth velocity for each patient is taken as the gradient of this slope (*e.g.* 5 cm·yr^{-1}). The greater the number of data points, the better the estimate of growth velocity. These data can then be analysed using analysis of covariance techniques including terms for congenital and environmental

Table 3. – Patient numbers required to detect between-group differences in growth velocity standard deviation score (SDS) for different types of growth study

Study type[#]	Study objective	Minimum detectable between-group difference SDS	Minimum number of patients per treatment group[¶]
1	Non-inferiority	0.3	525
1	Non-inferiority	0.4	296
1	Non-inferiority	0.5	189
2	Non-inferiority	0.3	525
2	Non-inferiority	0.4	296
2	Non-inferiority	0.5	189
3	Superiority	0.6	132
3	Superiority	0.8	74
3	Superiority	1.0	48
3	Non-inferiority	0.3	525
3	Non-inferiority	0.4	296
3	Non-inferiority	0.5	189

[#]: See figure 1 for growth study design classification (*i.e.* types 1–4); [¶]: based on 90% power, 5% significance level and standard deviation of not more than 1.5 SDS [34, 50].

factors as described previously. A more elegant alternative, that eliminates the need to calculate a regression slope for each patient, is to fit a mixed effects model, where subject effects are assumed to be random and all other effects are considered as fixed. Height is regressed on treatment, time plus other covariates, and the treatment by time interaction tests whether the treatments have different effects on growth velocity. In this type of analysis, subjects with more variable data (perhaps due to fewer height measurements because of early withdrawal), are given less weight in the analysis. Care should be taken when employing this method if dropout from the trial is not random (*e.g.* due to inferior comparator treatment).

Childhood height and predicted final height. Childhood height and predicted final height are not recommended as parameters for primary end points, but as supporting analyses for study types 1–3, and type 4 studies not measuring final height. For childhood height, the principal aim is to detect any shift in patients' height centile during the study. This is achieved by comparing individual subjects' height centile at the beginning and end of the study. To analyse study data, height centile at the end of the study can be plotted against height centile at the outset of treatment, and the correlation can be compared between treatment groups. Additional analysis can be performed by comparing, using logistic regression analysis, the proportion of children in each treatment group whose height centile shifts by a predefined number of centiles after treatment. An increase in the proportion of children whose height fell by more than one centile, for example, suggests impaired growth.

Predicted final height data are analysed using the same principles as for childhood height.

Final height. For final-height studies, as with growth-velocity studies, the first step towards calculating patient numbers for adequate statistical power is to determine the smallest difference that is needed to establish superiority of one treatment over another. Based on clinical experience and evidence from previous studies, a difference in final height of 5 cm would seem appropriate and reasonably convincing as a potential treatment effect. Final height studies (type 4) should be designed to establish noninferiority and therefore, in keeping with the principles applied for growth velocity described earlier, the equivalence range should be half the treatment effect. As previously mentioned, however, the validity of applying principles from efficacy studies to this setting is not known. Table 4 provides an indication of the patient numbers required to establish noninferiority for a series of minimum detectable differences, with 90% power and based on a standard deviation of $\leqslant$7.5 cm (the standard deviation for final height studies ranged from 4.8 to 7.5 cm, reflecting a lack of consistency in the design of these studies) [24, 52–55]. Using a childhood prediction of final height reduces the variability, and previous studies indicate that final height minus predicted final height has a standard

Table 4. – Patient numbers required to establish non-inferiority in final height studies

Minimum detectable difference cm	Minimum number of patients per treatment group[#]
1	1182
2	296
3	132
4	74
5	48

[#]: Based on 90% power, 5% significance level and standard deviation of not more than 7.5 cm [24, 51, 52, 54].

deviation of $\leqslant$6.0 cm [53, 54]. This reduction in standard deviation may appear small, but the two studies for which predicted final height data are available did not use skeletal age in the prediction, and the study protocols were not wholly stringent. Nevertheless, as shown in table 5, the numbers of patients needed to power the study decreased by approximately one-third compared with studies without final height prediction.

If predicted final height is measured for participants in final-height studies, the main aim of data analysis is to firstly obtain a comparison of actual *versus* predicted final height for each patient, and then compare treatments by assessing whether one treatment group creates a greater shortfall from predicted final height. In the absence of predicted height data, it is only possible to compare the final-height data between the treatment groups. Gender and nationality should be accounted for in the analysis, either through the use of final height SDS scores or as covariates in the statistical model. Analysis of covariance techniques should be used to compare treatment groups for both final height and actual *versus* predicted final height, including appropriate environmental covariates.

Populations to be analysed. Both the intent-to-treat and per-protocol populations should be analysed in all growth studies (the per-protocol population should be predefined at the start of the study and should exclude any protocol violations that could affect patients' growth assessment).

For study types 1–3, it is recommended that subjects who reach puberty at any point during the study are excluded from all data analysis, because of the marked and often unpredictable effects that this

Table 5. – Patient numbers required to establish non-inferiority in studies using final height minus predicted final height

Minimum detectable difference cm	Minimum number of patients per treatment group[#]
1	756
2	189
3	84
4	48
5	31

[#]: Based on 90% power, 5% significance level and standard deviation of not more than 6.0 cm [53, 54].

physiological state has on growth (prepubertal slowing and pubertal growth spurt), potentially confounding treatment effects. An interesting alternative would be to analyse the results of subjects going into puberty during the study separately, with the specific aim of increasing understanding of any potential effects of corticosteroids on growth during puberty.

For subjects discontinuing study therapy, postwithdrawal growth data for the entire study duration should be included, if possible, in a supplementary mixed-model analysis, as this can eliminate some of the problems arising from a higher dropout rate in the control population. This approach may also provide comparative "real-life" data with alternative therapies that are used in clinical practice.

Possible effects of the degree of asthma control on growth velocity should also be considered. For example, subanalysis of growth data could be carried out according to the number of exacerbations or a predefined level of asthma control, particularly taking into account the level of exercise and normal physical activities that the subjects engage in (although such analysis needs to be stated *a priori*). Asthma control should therefore be recorded during the study according to predefined criteria.

Conclusions

A large number of factors can potentially confound the results of studies assessing the effect of inhaled corticosteroid treatment on growth in children with asthma and it is important to be aware of all these factors when designing or interpreting such studies. The study objectives affect the influence of some confounding factors and the present authors have devised a new and simple classification system for growth studies to assist in the development of design recommendations that are appropriate for individual studies. The next step is to apply these principles to the interpretation of previously published growth studies, and this is the aim of the second part of this review.

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