START CARE: a protocol for an RCT of step-wise budesonide-formoterol reliever-based treatment in children


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START CARE: a protocol for an RCT of step-wise budesonide-formoterol reliever-based treatment in children

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“Take home message”: This protocol describes the first randomised controlled trial to compare the efficacy and safety of a step-wise budesonide-formoterol reliever-based regimen with conventional asthma therapy in children aged 5 to 11 years, addressing a gap in the literature (256 characters)
Abstract
Background
Asthma is the most common chronic childhood respiratory condition globally. Inhaled corticosteroid (ICS)-formoterol reliever-based regimens reduce the risk of asthma exacerbations compared with conventional short-acting beta₂-agonist (SABA) reliever-based regimens in adults and adolescents. The current limited evidence for anti-inflammatory reliever (AIR) therapy in children means it is unknown whether these findings are also applicable to children. High-quality randomised controlled trials (RCTs) are needed.

Objective
The study aim is to determine the efficacy and safety of budesonide-formoterol reliever alone or maintenance and reliever therapy (MART) compared with standard therapy: budesonide or budesonide-formoterol maintenance, both with terbutaline reliever, in children aged 5 to 11 years with mild, moderate and severe asthma.

Methods
A 52 week, multicentre, open-label, parallel group, phase III, two-sided superiority RCT will recruit 400 children aged 5 to 11 years with asthma. Participants will be randomised 1:1 to either budesonide-formoterol 100/6µg Turbuhaler reliever alone or MART; or budesonide or budesonide-formoterol Turbuhaler maintenance, with terbutaline Turbuhaler reliever. The primary outcome is moderate and severe asthma exacerbations as rate per participant per year. Secondary outcomes are asthma control, lung function, exhaled nitric oxide and treatment step change. Assessment of Turbuhaler technique and cost-effectiveness analysis are also planned.

Conclusion
This will be the first RCT to compare the efficacy and safety of a step-wise budesonide-formoterol reliever alone or MART regimen with conventional inhaled ICS or ICS-long-acting beta-agonist (LABA) maintenance plus SABA reliever in children. The results will provide a much-needed evidence base for the treatment of asthma in children.

Introduction
Background and rationale
Asthma is the most common chronic childhood respiratory condition worldwide, affecting an estimated 14% of children [1, 2]. Inhaled corticosteroid (ICS)-formoterol is the Global Initiative for Asthma (GINA) preferred reliever therapy in adolescents and adults across all treatment steps [3]. This approach has been termed anti-inflammatory reliever (AIR) therapy and relates to both ICS-formoterol reliever alone and maintenance and reliever therapy (MART).

At GINA Steps 1 and 2, the use of ICS-formoterol reliever as a sole therapy in adolescents and adults, reduces the risk of a severe asthma exacerbation by at least half (Odds ratio (OR) 0.45, 95% CI 0.34-0.60) compared with short-acting beta₂-agonist (SABA)-only reliever therapy [4]. Compared with low dose ICS plus SABA reliever, ICS-formoterol reliever as sole therapy resulted in a non-significant reduction in severe exacerbation risk (OR 0.79, 95% CI 0.59-1.07), and a significant reduced risk of an asthma-related hospital admission or emergency department or urgent care visit (OR 0.63, 95% CI 0.44-0.91).

At GINA Steps 3 and 4, the use of ICS-formoterol as maintenance and reliever therapy (MART) in adolescents and adults reduces the risk of severe asthma exacerbations compared to SABA-based reliever regimens for each of: same ICS dose in combination ICS-long acting beta-agonist (LABA) as
maintenance therapy (Risk ratio (RR) 0.68, 95% CI 0.58-0.80); higher ICS dose in combination ICS-LABA as maintenance therapy (RR 0.77, 95% CI 0.60-0.98); same ICS dose as maintenance therapy (RR 0.64, 95% CI 0.53-0.78); and higher ICS dose as maintenance therapy (RR 0.59, 95% CI 0.49-0.71) [5]. Post-hoc analysis of budesonide-formoterol self-administered according to the MART regimen in adolescents aged 12 to 17 years showed an overall reduction in the risk of a first severe asthma exacerbation with a hazard ratio of 0.49 (95% CI 0.34-0.70) [6]. This was comparable efficacy to that observed in adults where the hazard ratio for time to first severe exacerbation was 0.65 (95% CI 0.05-0.72) [7].

In a paradigm shift in the treatment of paediatric asthma, GINA no longer recommend SABA monotherapy at any step of treatment in children aged 6 to 11 years, instead suggesting administration of a separate ICS alongside as-needed SABA reliever at Step 1 of treatment [3, 8, 9]. GINA also recommend the use of MART at Steps 3 to 5, based on a single subgroup analysis of a larger study, which reported the safety and efficacy of ICS-formoterol MART in children aged 4 to 11 years [10]. ICS-formoterol MART reduced the risk of asthma exacerbations compared with same-dose maintenance ICS plus SABA reliever (RR 0.28, 95% CI 0.14-0.53) and higher-dose ICS plus SABA reliever (RR 0.43, 95% CI 0.21-0.87). These point estimates in children were greater than those observed in the larger study including adolescents and adults [11], (RR 0.64, 95% CI 0.53-0.78 and RR 0.77, 95% CI 0.60-0.98 respectively) indicating a potentially greater efficacy of this regimen in children. Because there has only been one study of ICS-formoterol MART the overall certainty of evidence for this regimen in children age 5 to 11 years is low.

We hypothesise that the step-wise use of budesonide-formoterol reliever alone, or as MART will have greater efficacy and a favourable safety profile compared with the step-wise use of standard budesonide or budesonide-formoterol maintenance both with terbutaline reliever, in children aged 5 to 11 years with mild, moderate and severe asthma.

Objective
The primary objective is to determine the efficacy and safety of budesonide-formoterol reliever alone, or together with maintenance treatment compared with standard therapy; budesonide or budesonide-formoterol maintenance, both with terbutaline reliever, in children aged 5 to 11 years with mild, moderate and severe asthma.

Methods
Study design
The STep-wise Anti-inflammatory Reliever Therapy Children’s Asthma Research (START CARE) study is an Investigator-initiated, 52-week, multicentre, open-label, parallel group, phase III, two-sided superiority RCT based in New Zealand (figure 1).

The Medical Research Institute of New Zealand (MRINZ) is the sponsor of the study, which is conducted with support from AstraZeneca Ltd., by both supply of randomised medications and funding of the study. AstraZeneca was consulted on the design of the trial and the writing of the protocol. They will have no role in the collection, analysis and interpretation of the data; or the decision to submit manuscripts for publication.

The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622001217796p). It was approved by the Northern B Health and Disability Ethics Committee, New Zealand (2022 FULL 13221). Regulatory approval for the use of the terbutaline 500µg in New Zealand was granted by the Standing Committee on Therapeutic Trials (2022 SCOTT 13289). The first study participant was enrolled in December 2022.
Participants and recruitment
A total of 400 participants aged 5 to 11 years with asthma (diagnosed by a doctor), using ICS or ICS-LABA as maintenance therapy plus a SABA reliever will be recruited at clinical trial sites and primary care-based research centres in New Zealand. Participants will be identified from clinical trial unit databases, general practices, mailouts and through direct advertising. Those who are potentially eligible (table 1) will be invited to attend an initial assessment visit.

Both informed consent of a parent/guardian and assent of the child participant will be required prior to enrolment.

Eligibility will be formally assessed on enrolment. Once eligibility is confirmed, participants will enter a four-week run-in period, at the GINA Step determined by the dose regimen of their pre-study asthma medication [3].

Turbuhaler technique assessment
As part of the eligibility assessment, participants will receive education and training on how to correctly use a Turbuhaler. Participants will be required to demonstrate an inspiratory flow rate of 30 to 90 L/min using an In-Check DIAL G16® device (Clement Clarke International, Essex, UK), and satisfactory inhaler technique using a Turbuhaler demonstration device (AstraZeneca, Södertälje, Sweden). Participants unable to demonstrate satisfactory inspiratory flow or inhaler technique at Visit 1 will not enter the run-in period. Those unable to demonstrate adequate technique at Visit 2 or who have two moderate or one severe asthma exacerbation during the run-in period will not be randomised.

Interventions
Participants will be randomised 1:1 to receive step-wise treatment of their asthma:

1. Intervention: budesonide-formoterol (Symbicort Turbuhaler®, AstraZeneca) 100/6µg dry powder reliever and/or maintenance.
2. Control: budesonide (Pulmicort Turbuhaler®, AstraZeneca) 100µg dry powder inhaler or budesonide-formoterol (Symbicort Turbuhaler®, AstraZeneca) 100/6µg maintenance, with Terbutaline (Bricanyl Turbuhaler®, AstraZeneca) 500µg dry powder inhaler one inhalation as-needed.

Investigators will escalate treatment following one severe, or two moderate asthma exacerbations, using treatment arm-specific step-wise algorithms (figure 2). In line with the current New Zealand asthma guidelines [12], participants in the control arm taking budesonide maintenance will increase to budesonide-formoterol as maintenance with terbutaline reliever if they require treatment escalation. Participants allocated to the intervention arm will be escalated from a paediatric adjusted budesonide-formoterol reliever alone regimen at Step 2, to very-low-dose MART at Step 3 and low-dose MART at Step 4. This aligns with GINA guidelines for adolescents and adults, and children over six years of age [3].

The participant will remain under the care of their usual healthcare provider for both acute and routine asthma management whilst enrolled in the study. Their usual healthcare provider will make treatment decisions during exacerbations and may increase their treatment for other reasons, including poor asthma symptom control. In these instances, the Investigator will maintain the escalation of treatment and ensure that it is in keeping with the randomised study treatment algorithms.
To maintain the pragmatic design of the study adherence to maintenance therapy will not be assessed for either the control or the intervention arm. Participants will not be asked to keep a diary and e-monitors of randomised medication will not be used.

Outcome measures
The primary outcome is asthma exacerbations as a rate per participant per year. This encompasses both moderate and severe exacerbations in accordance with recommendations of the American Thoracic Society/European Respiratory Society (ATS/ERS) [13]:

1. Severe asthma exacerbation: worsening asthma leading to either: an urgent, unplanned medical review (e.g. primary care or emergency department) or hospital admission; resulting in an acute prescription of systemic corticosteroids (tablets, suspension or injection); or, the use of corticosteroids for 3 or more days; or a hospital admission ≥24 hours.
2. Moderate asthma exacerbation: worsening asthma leading to either: an urgent, unplanned medical review or hospital admission for less than 24 hours; not resulting in an acute prescription of systemic corticosteroids; or, the use of systemic corticosteroids for less than 3 days, which does not meet the criteria for a severe exacerbation (e.g. use of systemic corticosteroids from a non-acute prescription, such as a home supply or delayed script).

For an asthma exacerbation to be considered as a separate event, it must be preceded by at least 7 days during which none of the above criteria for an asthma exacerbation are fulfilled.

Collection of data relevant to the primary outcome is through participant and/or parent/guardian report. Participant medical records will be used to confirm missing data.

Secondary outcome measures including length of hospital stay, systemic corticosteroid dose and growth (table 2) have been chosen to provide clinically relevant information on efficacy and safety of the randomised treatments. A cost-effectiveness analysis is also planned.

Trial procedures
Participants will attend a total of six study visits over a 56-week period (table 3). All visits will be conducted in-person at a trial site.

Asthma control will be assessed using the Asthma Control Questionnaire (ACQ-5, symptoms-only version) [14] at visits 2, 4 and 6. The interviewer-administered version will be used for all participants [15]. At visits 2, 4 and 6, fractional exhaled nitric oxide (FeNO) – a biomarker of Type 2 inflammation – will be measured in accordance with ATS guidelines [16], using a NIOX VERO® device (Circassia AB, Uppsala, Sweden). On-treatment forced expiratory volume in one second (FEV₁) will be measured at visits 2, 4 and 6 using an Easy-on-PC® Spirometer (NDD Medical Technologies, Zurich, Switzerland). Reversibility testing will not be performed. Spirometry results will be interpreted according to ATS/ERS criteria [17], using Global Lung Function Initiative (GLI) reference ranges [18].

Participants will be issued with study inhalers at each visit. All participants and their parent(s)/guardian(s) will be educated on correct medication use and inhaler technique at visit 1, with subsequent education and training provided at each study visit. Participants will also receive a written asthma action plan detailing how to use their inhalers and when to seek medical help (supplementary material). These plans have been adapted from the Asthma and Respiratory Foundation New Zealand action plans and are similar to those used in the Children’s Anti-inflammatory RELiever (CARE) study [19–21]. The reverse of each action plan contains a log for participants and their parent(s)/guardian(s) to record details of asthma-related events, including medical reviews, prescription changes, and time off work and/or school due to asthma.
Participants may attend additional, unscheduled visits at their request or at the request of an Investigator. Reasons for additional visits include: for treatment escalation following a severe exacerbation, the need for additional study medication and consideration of withdrawal.

Following study completion, participants will be provided with post-trial treatment. This will be selected with consideration of the New Zealand asthma guidelines and the preferences of the participant and their parent/guardian. No post-trial follow-up is planned.

Sample size
By simulation from appropriate Poisson distributions, we estimate 320 participants are required to detect a difference in asthma exacerbation rates between 1.0 in the control arm and 0.67 in the intervention arm; rate ratio 0.67, with 90% power and two-sided $\alpha$ of 5%. Assuming a dropout rate of 20%, a total of 400 participants (200 in each arm) will be recruited.

Randomisation
Randomisation will be performed using a computer-generated sequence to maintain allocation concealment. This will be generated by the study statistician, independent of the Investigators. Block size will vary by site. Randomisation will be stratified according to:

- History of a severe asthma attack in the preceding 12 months (0 or $\geq$1)
- GINA treatment step (Step 2 or $>$ Step 2)

Participants in the same primary household are able to be enrolled in the study (supplementary material).

Allocation concealment and blinding
This is an open-label study in which the participants, their parent(s)/guardian(s), and the study team are aware of the randomised treatment. A participant’s treatment allocation will only be revealed to the Investigators when that participant is randomised.

Data collection
Data will be collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the Medical Research Institute of New Zealand (MRINZ) [22, 23]. A REDCap-based Clinical Data Management Application (CDMA) will facilitate the electronic collection of data during study visits. Data will be collected via participant logs and through participant and/or parent/guardian-report at each visit.

Statistical methods
The analysis of the primary outcome variable, the count of asthma exacerbations in relation to the time of observation in the study, will be by estimation of the relative rate of total asthma exacerbations per participant per year. This will be by Poisson regression with an offset for the time of observation and a fixed effect of randomised treatment allocation. Over-dispersion will be evaluated prior to analysis and a corrected analysis applied if necessary.

A sensitivity analysis will include the following potentially important predictors of response at baseline: age, sex, ethnicity, ACQ-5 score, GINA Step (2 or $\geq$2), FeNO, trial site, and the number of severe asthma exacerbations in the previous 12 months, to account for possibly different distributions of these variables in the treatment groups. The planned analysis approaches for the secondary outcome variables are shown in table S1 (supplementary material).

Treatment modification effects (sub-group analyses) will use appropriate interaction terms for the primary outcome variable with estimation of treatment differences within sub-groups, and
illustrated by a ‘Forest’ plot. The treatment modification variables will be: severe asthma exacerbation in the 12 months prior to enrolment, age at enrolment, sex, ethnicity, smoking exposure, ACQ-5 score at randomisation (for asthma exacerbations and severe asthma exacerbations outcomes only), FeNO at randomisation, FEV1 % predicted at randomisation, and treatment step at randomisation.

The statistical analysis will be by intention-to-treat by a biostatistician masked as to treatment allocation. SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) will be used.

Cost-effectiveness analysis
The incremental cost per moderate and/or severe exacerbation averted will be reported (supplementary material).

Device preferences survey
Participants and parent(s)/guardian(s) of participants enrolled at selected sites will be asked to participate in the device preferences survey. This will provide data on whether participants and their parent(s)/guardian(s) consider the Turbuhaler an acceptable alternative to a metered dose inhaler (MDI) and spacer.

Data and safety monitoring
Adverse events (AE) will be reported to the sponsor within 5 working days of a site obtaining the data. These will be reviewed by a central medical monitor weekly and by the medical terminology assigners, and the study monitor. All sites will respond to queries raised following these reviews within 5 working days. A summary of AEs is provided to the Data and Safety Monitoring Committee (DSMC) monthly.

The sponsor will be notified directly when an asthma exacerbation event is entered by an automatically generated email from the CDMA. These events will be reviewed monthly by the sponsor site to ensure that they have been correctly identified and allocated to either moderate or severe categories.

Serious adverse events (SAE) will be reported to the sponsor with 24 hours of a site becoming aware of the event. The primary mechanism for this reporting is through the CDMA. There will be an expedited medical monitor review process for these events and sites must respond to queries raised within 2 working days. The sponsor will notify the DSMC of the event and provide all available data within 72 hours of receiving a notification.

An independent DSMC has been established, with membership comprising clinicians with expertise in paediatric and respiratory medicine, and research experience.

The DSMC will review all serious adverse events on an expedited basis (with 72 hours). They will undertake a formal review of enrolments, withdrawals, and adverse events every six months to ensure adequate safety and minimal risk to participants. Where they consider that there may be an impact on the ethical conduct of the trial or the scientific validity of the trial results they will make recommendations. These recommendations will be reviewed by the trial management group (TMG) and the trial steering committee (TSC), who will decide on implementation either in part or in full. The DSMC may recommend termination of the trial, however the TSC will make the final decision.

Discussion
This study will be first RCT of a step-wise approach to ICS-formoterol reliever-based therapies in children with mild, moderate and severe asthma aged 5 to 11 years. If comparable efficacy in
reducing asthma exacerbations is demonstrated in childhood asthma as in adolescents and adults, then implementation of this regimen would potentially reduce the burden of asthma in children globally.

The primary outcome of asthma exacerbations as a rate per participant was chosen as asthma exacerbation prevention is a key tenet of asthma management, with rate the preferred measure in clinical trials. The criteria for moderate and severe exacerbations are also based on the ATS/ERS recommendations for standardising endpoints in clinical trials [13].

The age range of 5 to 11 years was in keeping with the New Zealand child asthma and GINA guidelines at the time of study development. Around half of children under the age of 5 years who wheeze, no longer do so at school age, which creates a challenge in determining whether wheeze in this age group represents a diagnosis of asthma [3, 12]. It also recognises the already substantive evidence of the efficacy of budesonide-formoterol reliever-based regimens in adolescents 12 years and above [6].

The study will extend the single subgroup analysis findings of Bisgaard and colleagues [10], who examined an ultralow dose MART regimen (budesonide-formoterol 100/6µg once daily maintenance plus additional inhalations for symptom relief), in children 4 to 11 years old. This MART regimen is used at Step 3 in our step-wise algorithm, with provision of one higher dose MART regimen for children with more severe asthma at Step 4 and a reliever alone regimen for those with milder asthma entering at Step 2. The corresponding treatment steps in the control regimen use twice the dose of maintenance ICS at both Steps 3 and 4 and require regular budesonide 100µg twice daily for those at Step 2 (figure 2). It will also complement the CARE study of budesonide-formoterol reliever alone versus salbutamol reliever alone in children aged 5 to 15 years with mild asthma currently being undertaken by the MRINZ [21].

Important features of the study are the ability to make comparisons across multiple treatment steps, rather than one direct comparison at a single step as undertaken in the adult and adolescent studies, and to escalate treatment in response to severe exacerbations or multiple moderate exacerbations. The stepwise algorithm was based on the 2021 GINA strategy for children [24]. It could be argued that the regimens preferentially favour the control arm in that higher maintenance ICS doses are prescribed at each step. However, this decision was made due to: the evidence that the timing of the ICS-formoterol dose is more important than the total daily dose in determining efficacy in adult asthma [25, 26], the relatively flat therapeutic dose response relationship with ICS treatment in children [27], and to reduce the risk of systemic side effects.

Blinding was impractical for a number of reasons. Firstly, the inhaler for each medication is identified by a different coloured base, and the option of standardising this was not available. Secondly, the maintenance medication dosing differs between the control and intervention arm with higher doses of ICS at all steps in the control arm making it impossible to conceal the treatment arm from investigators. Thirdly, the addition of placebo reliever inhalers in both arms would require participants to take two inhalations when required for symptom relief (one from each inhaler) increasing participant burden and markedly reducing the generalisability of the findings to routine clinical practice.

All participants will be issued with asthma action plans, adapted from the Asthma and Respiratory Foundation of New Zealand action plans [19, 20]. It is recommended participants in both arms seek help from their usual healthcare practitioner the same day if they use more than six inhalations of their reliever medication in 24h, and call an ambulance if they use more than eight inhalations. The
maximum daily dose of budesonide-formoterol (800/48µg) was determined based on the relative dose equivalence of repeated doses of formoterol 6µg with terbutaline 500µg and available regulatory safety datasheets [28, 29].

In conclusion, this Investigator-initiated RCT will be the first to compare the efficacy and safety of a step-wise budesonide-formoterol reliever-based regimen with conventional SABA reliever-based regimens in children with mild, moderate and severe asthma. It will fill an evidence gap in the literature, and determine whether the efficacy of ICS-formoterol reliever-based regimens in adolescents and adults also applies to children.

Figure 1: Participant timeline

Figure 2: START CARE step-wise algorithms. a) Treatment algorithm followed by participants during the run-in period and in the control group. Participants will take budesonide 100µcg (one to two inhalations, twice daily) or budesonide-formoterol 100/6µcg (one to two inhalations, twice daily) maintenance, with terbutaline 500µcg (one inhalation as needed) reliever. Dose determined by GINA Step at entry. b) Treatment algorithm followed by participants in the intervention group. Participants will take budesonide-formoterol 100/6µcg (one inhalation as needed) reliever at all Steps, and at Steps 3 and 4 budesonide-formoterol 100/6µcg (one inhalation, one to two times daily) as maintenance. Dose determined by GINA Step at entry. GINA: Global Initiative for Asthma.
<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Patients of any gender age 5 to 11 years (inclusive) at Visit 1</td>
<td>Already using ICS-formoterol or ICS-salbutamol as a reliever</td>
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<tr>
<td>Doctor diagnosis of asthma (self-report by parent/participant or healthcare provider-reported)</td>
<td>Any use of high dose ICS-LABA (New Zealand Child Asthma Guidelines Step 5), [12] biologics, maintenance oral corticosteroids (i.e. GINA Step 5), [3] or leukotriene receptor antagonists in the last 6 months</td>
</tr>
<tr>
<td>Use of ICS or ICS-LABA maintenance plus SABA reliever therapy (corresponding to GINA step 2, 3 or 4) [3], in the 6 months prior to Visit 1</td>
<td>Any use of systemic corticosteroids in the 6 weeks prior to Visit 1</td>
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<td>Registered with a General Practitioner</td>
<td>Use of a beta-blocker in the 6 months prior to Visit 1</td>
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<td>Satisfactory Turbuhaler technique</td>
<td>Any medical condition which, at the Investigator’s discretion, may present a safety risk or impact the feasibility of the study or study results (including but not limited to, other significant respiratory comorbidities, such as cystic fibrosis and bronchiectasis)</td>
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<td>Inspiratory flow measurement of between 30 and 90 L/min</td>
<td>Any known or suspected hypersensitivity (including rash, urticaria, angioedema, bronchospasm and anaphylactic reaction) to the active substances prescribed in the study (budesonide, formoterol, terbutaline), lactose or milk protein (excipient)</td>
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<tr>
<td>Provision of written informed consent (parent/guardian) and assent (participant)</td>
<td>Any intravenous therapy for the treatment of asthma, in the last year</td>
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<td>Able and willing to switch from current treatment regimen</td>
<td>Previous Intensive Care Unit admission for asthma, or ventilation for asthma, ever</td>
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<td>For randomisation at Visit 2, participants should fulfil the following criteria:</td>
<td>Participation in another clinical trial of a medicinal product in the 30 days prior to Visit 1</td>
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<tr>
<td>Satisfactory Turbuhaler technique</td>
<td>Any severe exacerbation, or 2 moderate exacerbations (per protocol defined criteria) and/or a change in asthma treatment other</td>
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<tr>
<td>Objectives</td>
<td>Outcome measures</td>
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<td><strong>Primary objective</strong></td>
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<td>To compare the efficacy and safety of budesonide-formoterol maintenance</td>
<td>Asthma exacerbations (moderate and severe) as a rate per participant per year</td>
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<td>and/or reliever therapy versus standard therapy: budesonide maintenance</td>
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<td>or budesonide-formoterol maintenance, both with terbutaline reliever</td>
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<td><strong>Secondary objectives</strong></td>
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<tr>
<td>To compare the efficacy of budesonide-formoterol maintenance and/or</td>
<td>Proportion of participants with at least one asthma exacerbation (moderate or</td>
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<td>reliever therapy versus standard therapy: budesonide maintenance or</td>
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<td>budesonide-formoterol maintenance, both with terbutaline reliever</td>
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<td>Proportion of participants with at least one severe exacerbation</td>
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<td>Proportion of participants with at least one step up in treatment</td>
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<td>Proportion of participants on each treatment step</td>
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<td>Severe asthma exacerbations as a rate per participant per year</td>
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<td>Composite of asthma exacerbations (moderate and severe), or step up in</td>
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<td>treatment as a rate per participant per year</td>
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<td>Proportion of participants with at least one asthma exacerbation (moderate</td>
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<td>or severe), or step up in treatment</td>
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<tr>
<td>Step up in treatment, as a rate per participant per year</td>
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ICS: inhaled corticosteroid; LABA: long acting beta-agonist; SABA: short acting beta-agonist; GINA: Global Initiative for Asthma
<table>
<thead>
<tr>
<th>Variable</th>
<th>Time/Length</th>
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<tr>
<td>Time to first moderate or severe exacerbation</td>
<td>Variable</td>
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<tr>
<td>Time to first severe asthma exacerbation</td>
<td>Variable</td>
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<tr>
<td>Time to first exacerbation (moderate or severe), or step up in treatment</td>
<td>Variable</td>
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<tr>
<td>Time to first step up in treatment</td>
<td>Variable</td>
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<tr>
<td>Fractional exhaled nitric oxide (FeNO)</td>
<td>1, 26 and 52 weeks</td>
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<tr>
<td>On-treatment forced expiratory volume in one second (FEV₁)</td>
<td>1, 26, and 52 weeks</td>
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<td>Days in hospital</td>
<td>52 weeks</td>
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<td>Days lost from school due to asthma</td>
<td>52 weeks</td>
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<td>Days lost from usual activities due to childcare for asthma (parent(s)/guardian(s))</td>
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</tr>
<tr>
<td>Asthma Control Questionnaire 5 (ACQ-5)</td>
<td>1, 26 and 52 weeks</td>
</tr>
<tr>
<td>To compare the safety of budesonide-formoterol maintenance and/or reliever therapy versus standard therapy: budesonide maintenance or budesonide-formoterol maintenance, both with terbutaline reliever</td>
<td>Total systemic corticosteroid dose 52 weeks</td>
</tr>
<tr>
<td>Change in height from randomisation to study completion</td>
<td>13, 26, 39 and 52 weeks</td>
</tr>
<tr>
<td>Number and proportion of Adverse Events (AEs)</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Number and proportion of Serious Adverse Events (SAEs)</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Proportion of participants who discontinue treatment or withdraw</td>
<td>52 weeks</td>
</tr>
<tr>
<td>To assess the ability of children to successfully use the Turbuhaler device</td>
<td>Proportion of participants withdrawn due to inability to use the Turbuhaler device 52 weeks</td>
</tr>
<tr>
<td>Number of Turbuhaler retraining events required at each study visit</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Inspiratory flow rate at each study visit</td>
<td>52 weeks</td>
</tr>
<tr>
<td>To compare the cost effectiveness of budesonide-formoterol maintenance and/or reliever therapy versus standard therapy: budesonide maintenance or budesonide-formoterol maintenance, both with terbutaline reliever</td>
<td>Incremental cost per moderate and/or severe exacerbation averted 52 weeks</td>
</tr>
<tr>
<td>Table 3 Schedule of trial procedures</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Visit</strong></td>
<td><strong>Enrolment/run-in</strong></td>
</tr>
<tr>
<td>Day</td>
<td>1</td>
</tr>
<tr>
<td>Window</td>
<td>N/A</td>
</tr>
<tr>
<td>Confirm informed consent/assent</td>
<td>X</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
</tr>
<tr>
<td>Asthma history</td>
<td>X</td>
</tr>
<tr>
<td>Turbuhaler training and assessment of technique</td>
<td>X</td>
</tr>
<tr>
<td>Run-in inhalers</td>
<td>d</td>
</tr>
<tr>
<td>Randomisation</td>
<td>X</td>
</tr>
<tr>
<td>Height and weight</td>
<td>X</td>
</tr>
<tr>
<td>ACQ-5 (IA)</td>
<td>X</td>
</tr>
<tr>
<td>Health economics data</td>
<td>X</td>
</tr>
<tr>
<td>FeNO*</td>
<td>X</td>
</tr>
<tr>
<td>FEV₁</td>
<td>X</td>
</tr>
<tr>
<td>Preferences survey*</td>
<td>X</td>
</tr>
<tr>
<td>Dispense trial medication</td>
<td>d</td>
</tr>
<tr>
<td>SAE/AE review</td>
<td>X</td>
</tr>
<tr>
<td>Asthma review</td>
<td>X</td>
</tr>
<tr>
<td>Asthma exacerbations</td>
<td>X</td>
</tr>
<tr>
<td>Asthma action plan and log sheet education and (re-)issue</td>
<td>X</td>
</tr>
<tr>
<td>GP communications</td>
<td>X</td>
</tr>
<tr>
<td>Dispense/prescribe post-trial medication</td>
<td></td>
</tr>
<tr>
<td>Provide parent/participant reimbursement and gift</td>
<td>X</td>
</tr>
</tbody>
</table>

ACQ-5 (IA): Asthma Control Questionnaire, Investigator Administered; FeNO: Fractional exhaled nitric oxide; FEV₁: Forced expiratory volume in 1 sec; SAE: serious adverse event; AE: adverse event; GP: General Practitioner, d: dispensed; r: return; c: check.*: FeNO must be performed before FEV₁. “+”: selected sites only.


Figure 1

Run-in period

Week -4

Screening, consent and enrolment

Week 0

Randomisation

Budesonide-formoterol 100/6μg reliever alone or MART per GINA Step (n=200)

Intervention period

Week 52

Completion

Budesonide 100μg or budesonide-formoterol 100/6μg maintenance plus as needed terbutaline 500μg per GINA Step (n=200)

V1 Day -28

V2 Day 0

V3 Day 91

V4 Day 182

V5 Day 273

V6 Day 365
Figure 2

a. Regular

Step 1
Budesonide 100µg, 1 inhalation twice daily

Step 2
Budesonide-formoterol 100/6µg, 1 inhalation twice daily
OR
Budesonide 100µg, 2 inhalations twice daily

Step 3
Budesonide-formoterol 100/6µg, 2 inhalations twice daily

Step 4
Budesonide-formoterol 100/6µg, 1 inhalation twice daily

Reliever
Terbutaline 500µg, 1 inhalation as needed

b.

Step 1
None

Step 2
Budesonide-formoterol 100/6µg, 1 inhalation once daily

Step 3
Budesonide-formoterol 100/6µg, 1 inhalation twice daily

Step 4
Budesonide-formoterol 100/6µg, 1 inhalation as needed

Reliever
Budesonide-formoterol 100/6µg, 1 inhalation as needed

Figure 2
START CARE: A protocol for an RCT of step-wise budesonide-formoterol reliever-based treatment in children

Supplementary Material

Table S1 Secondary outcome variable analysis ............................................................... 2
Figure S1 Control arm (terbutaline reliever) ................................................................. 3
Figure S2 Intervention arm (budesonide-formoterol reliever) ..................................... 5
Randomisation ............................................................................................................. 7
Cost effectiveness analysis ....................................................................................... 7
<table>
<thead>
<tr>
<th><strong>Method of analysis</strong></th>
<th><strong>Secondary outcome variables</strong></th>
</tr>
</thead>
</table>
| Poisson regression with an offset for the time of observation and a fixed effect of randomised treatment allocation | Severe asthma exacerbations per participant per year  
Composite of asthma exacerbations (moderate and severe), or step up in treatment as a rate per participant per year  
Step up in treatment, as a rate per participant per year  
Number of days lost from school due to asthma (participant)  
Number of days lost from usual activities due to childcare for asthma (parent(s)/guardian(s))  
Number of days in hospital* |
| Comparison of proportions by logistic regression | The proportion of participants with at least one asthma exacerbation  
The proportion of participants with at least one severe asthma exacerbation  
The proportion of participants with at least one step up in treatment, with baseline GINA step as covariate  
The proportion of participants discontinued from treatment and reason  
The proportion of participants withdrawn and reason  
Adverse events  
Serious adverse events |
| Survival analysis illustrated by Kaplan-Meier plots and use of Cox’s proportional hazards regression to estimate the hazard ratio in relation to the randomised treatment | Time to first asthma exacerbation  
Time to first severe asthma exacerbation  
Time to first moderate or severe asthma exacerbation, or step up in treatment  
Time to first step up in treatment |
| ANCOVA with baseline (where available) as a continuous covariate | FEV₁  
FEV₁ z-score  
FEV₁% predicted  
FEV₁ prediction value (GLI values)  
FeNO (on the logarithm-transformed scale)  
Growth velocity |
| ANCOVA and mixed linear models for repeated measures by time | ACQ-5 |
| Analysis dependent on data distribution | Total systemic corticosteroid dose*  
Total number of courses of antibiotics for respiratory tract infections |

GINA: Global Initiative for Asthma; FEV₁: forced expiratory volume in 1 s; FeNO: fractional exhaled nitric oxide; ACQ-5: Asthma Control Questionnaire; *: data for the number of days in hospital is likely to be sparse. If it is not possible or appropriate to use Poisson regression, the data will be analysed separately. †: data for total systemic corticosteroid may be sparse. Methods that will be explored include: dichotomous variable “had course of oral steroids or not”; attempt at Mann-Whitney test with Hodges-Lehmann confidence interval; and Poisson regression, treating courses of oral steroids as a count variable.
Figure S1 Control arm (terbutaline reliever)

**Preventer inhaler**
Your preventer is ___________
You take this every day even when you are well.

**Reliever inhaler**
Your reliever is Bricanyl
You take this only when you need it.
You should carry your reliever with you at all times.

---

**Asthma Action Plan | Blue Plan**

**Name:**

**Date of plan:**

**GP:**

**GP phone:**

### Feeling well

**Your asthma is under control when...**
- You do not have asthma symptoms most days (wheeze, tight chest, cough, or find it hard to breathe)
- You can play just like other children
- Most days you do not need your reliever

**Remember...**

<table>
<thead>
<tr>
<th>Preventer</th>
<th>Reliever</th>
</tr>
</thead>
<tbody>
<tr>
<td>___ inhalation(s) every morning</td>
<td>1 inhalation when needed to relieve symptoms</td>
</tr>
<tr>
<td>___ inhalation(s) every night</td>
<td>Bricanyl</td>
</tr>
</tbody>
</table>

### Getting worse

**Your asthma is getting worse when...**
- You coughing or wheezing more
- OR you wake up at night because of your asthma
- OR You are using more than 4 inhalations of your reliever a day, for one week

**Let's take action...**
- You need to see your doctor within the next week to change your preventer
- Take 1 inhalation of your reliever as often as needed to relieve symptoms

### Feeling worried

**Your asthma is a worry when...**
- You are breathing fast or find it hard to breathe
- OR your reliever is only helping for 2-3 hours
- OR you are using more than 6 inhalations of your reliever a day
- OR you feel you need to see your doctor

**Let's get help...**
- You need to see your doctor or go to the hospital today
- Take 1 inhalation of your reliever as often as needed to relieve symptoms

### Emergency

**Your asthma is an emergency when...**
- Your symptoms are getting more severe quickly
- OR you are finding it hard to speak or breathe
- OR you look pale or blue
- OR your reliever is not helping
- OR you are using your reliever every 1-2 hours
- OR you are using more than 8 inhalations of your reliever a day

**Let's keep calm...**
- Dial 111 for an ambulance and tell them you're having a severe asthma attack
- Sit upright and try to stay calm
- Take 1 inhalation of your reliever as often as needed until help arrives
- Even if you seem to get better, seek medical help right away

**Medical help**
If you need medical help for your asthma, please contact your GP. After Hours service, or 111 as appropriate. This is important to make sure you get treated quickly.

**Next appointment dates**
- Visit 2 ___________
- Visit 3 ___________
- Visit 4 ___________
- Visit 5 ___________
- Visit 6 ___________

**Study contact**
Name ___________
Phone ___________
Email ___________
How to use your inhaler

1. Hold the inhaler upright and remove the cover
2. Check the dose counter just below the mouthpiece. Use a different inhaler if it is red.
3. Twist the red grip as far as it will go in one direction and then back again until you hear a click. Your inhaler is now ready to use.
4. Place the mouthpiece between your lips and suck in deeply and forcefully through your inhaler. (You may not taste or feel the medication.)
5. Remove the inhaler from your mouth and breathe out. Do not breathe back into the mouthpiece as you will make it damp inside.
6. If you need more, repeat the steps above.
7. When you are finished, place the cover back on the inhaler and twist shut.

Caring for your inhaler

1. Do not wash your inhaler as it will not work properly if it gets wet.
2. Wipe the mouthpiece with a dry tissue or cloth.

Since your last visit...

Have you taken any days off school or work due to asthma?

<table>
<thead>
<tr>
<th>Start date</th>
<th>End date</th>
<th>How many days off school?</th>
<th>Did someone take time off work due to your asthma?</th>
<th>How many people took time off work due to your asthma?</th>
<th>How many days did each person take off work?</th>
</tr>
</thead>
<tbody>
<tr>
<td>eg. 01/01/2023</td>
<td>eg. 03/03/2023</td>
<td>eg. 3</td>
<td>eg. Yes</td>
<td>eg. 2 - me and mum</td>
<td>eg. Me 2 days, Mum 1 day</td>
</tr>
</tbody>
</table>

Have you started any new medication (other than prednisone) OR changed any existing medication?

<table>
<thead>
<tr>
<th>Medication started/changed</th>
<th>Dose</th>
<th>How many times a day?</th>
<th>How long for?</th>
<th>Date started/changed</th>
<th>Date stopped</th>
<th>Reason for medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>eg. Amoxicillin</td>
<td>eg. 500mg</td>
<td>eg. 3</td>
<td>eg. 5 days</td>
<td>eg. <strong>9/9/2023</strong></td>
<td>eg. <strong>9/9/2023</strong></td>
<td>eg. Sore throat</td>
</tr>
</tbody>
</table>

Have you visited your doctor (e.g. GP) or been admitted to hospital due to asthma?

<table>
<thead>
<tr>
<th>Date</th>
<th>Service used?</th>
<th>Prednisone given?</th>
<th>Prednisolone dose?</th>
<th>How long for?</th>
<th>Start date</th>
<th>Stop date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>eg. 15/09/2023</td>
<td>eg. ED visit</td>
<td>eg. Yes</td>
<td>eg. 40mg</td>
<td>eg. *days</td>
<td>eg. 15/09/2020</td>
<td>eg. Admitted</td>
<td></td>
</tr>
</tbody>
</table>
**Figure S2 Intervention arm (budesonide-formoterol reliever)**

**Asthma Action Plan - Red Plan**

- **Feeling well**
  - **Your asthma is under control when...**
    - You do not have asthma symptoms most days (wheeze, tight chest, cough, or find it hard to breathe)
    - You can play just like other children
    - Most days you do not need to use your Symbicort as a reliever
  - **Know your asthma symptoms**
  - **Know when and how to take your inhaler**
  - **Remember...**
    - **Preventer and reliever:** ___ inhalation(s) every morning
    - Symbicort ___ inhalation(s) every night
    - 1 inhalation when needed to relieve symptoms

- **Getting worse**
  - **Your asthma is getting worse when...**
    - You coughing or wheezing more
    - OR you wake up at night because of your asthma
    - OR You are using more than 4 reliever inhalations a day, for one week
  - **Let's take action...**
    - You need to see your doctor within the next week to change the way you use your inhaler
    - Take 1 inhalation of your Symbicort as often as needed to relieve symptoms

- **Feeling worried**
  - **Your asthma is a worry when...**
    - You are breathing fast or find it hard to breathe
    - OR your Symbicort is only helping for 2-3 hours
    - OR you are using more than 6 reliever inhalations a day
    - OR you feel you need to see your doctor
  - **Let's get help...**
    - You need to see your doctor or go to the hospital today
    - Take 1 inhalation of your Symbicort as often as needed to relieve symptoms

- **Emergency**
  - **Your asthma is an emergency when...**
    - Your symptoms are getting more severe quickly
    - OR you are finding it hard to speak or breathe
    - OR you look pale or blue
    - OR your Symbicort is not helping
    - OR you are using your Symbicort every 1-2 hours
    - OR you are using more than 8 reliever inhalations a day
  - **Let's keep calm...**
    - Dial 111 for an ambulance and tell them you're having a severe asthma attack
    - Sit upright and try to stay calm
    - Take 1 inhalation of Symbicort as often as needed until help arrives
    - Even if you seem to get better, seek medical help right away

**Your inhaler...**
- Your Inhaler is Symbicort
- Symbicort is a preventer and a reliever inhaler
- You do not need an extra inhaler as a reliever
- You should carry your Symbicort with you at all times

**Next appointment dates**
- Visit 2 __________________
- Visit 3 __________________
- Visit 4 __________________
- Visit 5 __________________
- Visit 6 __________________

**Study contact**
- Name __________________
- Phone __________________
- Email __________________

**Medical help**
- If you need medical help for your asthma, please contact your GP. After Hours service, or 111 as appropriate.
- This is important to make sure you get treated quickly.
**How to use your inhaler**

1. Hold the inhaler upright and remove the cover.
2. Check the dose counter just below the mouthpiece. Use a different inhaler if it is red.
3. Twist the red grip as far as it will go in one direction and then back again until you hear a click. Your inhaler is now ready to use.
4. Place the mouthpiece between your lips and suck in deeply and forcefully through your inhaler. (You may not taste or feel the medication.)
5. Remove the inhaler from your mouth and breathe out. Do not breathe back into the mouthpiece as you will make it damp inside.
6. If you need more, repeat the steps above.
7. When you are finished, place the cover back on the inhaler and twist shut.

**Caring for your inhaler**

1. Do not wash your inhaler as it will not work properly if it gets wet.
2. Wipe the mouthpiece with a dry tissue or cloth.

---

**Since your last visit...**

**Have you taken any days off school or work due to asthma?**

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<th>End date</th>
<th>How many days off school?</th>
<th>Did someone take time off work due to your asthma?</th>
<th>How many people took time off work due to your asthma?</th>
<th>Who were they?</th>
<th>How many days did each person take off work?</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. 01/01/2023</td>
<td>e.g. 01/02/2023</td>
<td>e.g. 3</td>
<td>e.g. Yes</td>
<td>e.g. 2 - me and mum</td>
<td>e.g. Mr 2 days, Mrs 1 day</td>
<td></td>
</tr>
</tbody>
</table>

---

**Have you started any new medication (other than prednisone) OR changed any existing medication?**

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<thead>
<tr>
<th>Medication started changed</th>
<th>Dose</th>
<th>How many times a day?</th>
<th>How long for?</th>
<th>Date started/changed</th>
<th>Date stopped</th>
<th>Reason for medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. Amoxicillin</td>
<td>e.g. 500mg</td>
<td>e.g. 3</td>
<td>e.g. 5 days</td>
<td>e.g. 05/09/2023</td>
<td>e.g. 08/09/2023</td>
<td>e.g. Sore throat</td>
</tr>
</tbody>
</table>

---

**Have you visited your doctor (e.g. GP) or been admitted to hospital due to asthma?**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. 15/09/2022</td>
<td>e.g. ED visit</td>
<td>e.g. Yes</td>
<td>e.g. 40mg</td>
<td>e.g. 7 days</td>
<td></td>
<td>e.g. 15/09/2020</td>
<td>e.g. 18/09/2022</td>
<td>e.g. Admitted</td>
</tr>
</tbody>
</table>
Randomisation

Where two or more participants in the same primary household are enrolled in the study, they will be randomised separately. This is in recognition of the fact that parents/guardians often manage multiple different asthma plans within a household.

Cost effectiveness analysis

The probability that the intervention is cost-effective at various willingness-to-pay values for averting a moderate and/or severe exacerbation will be estimated by cost-effectiveness acceptability curves. The base-case analysis will take a health system perspective (asthma-related resource utilisation) in the 12-month follow-up period. Parent/guardian self-reported healthcare resource utilisation will consist of: asthma inhalers (dispensed); antibiotics; oral corticosteroids; general practice visits; after hours clinics; emergency department visits; paediatric outpatient visits; inpatients hospitalisations (admissions and days per admission). Secondary analysis will monetise time off school for the participant and time off work or usual activities, due to asthma caregiving, for parent(s)/guardian(s). Subgroup analysis will stratify the sample, as defined at randomisation, by mild, moderate and severe asthma.