START CARE: a protocol for a randomised controlled trial of step-wise budesonide–formoterol reliever-based treatment in children

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Shareable abstract (@ERSpublications)
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 5–11 years, addressing a gap in the literature https://bit.ly/3SMNdS6

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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 β_2-agonist (SABA) reliever-based regimens in adults and adolescents. The current limited evidence for anti-inflammatory reliever 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 100/6 µg 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 β-agonist 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 β_2-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 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 β-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 aged 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 randomised controlled trial (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 500 µg in New Zealand was granted by the Standing Committee on Therapeutic Trials (2022 SCOTT 13289). The first study participant was enrolled in December 2022.

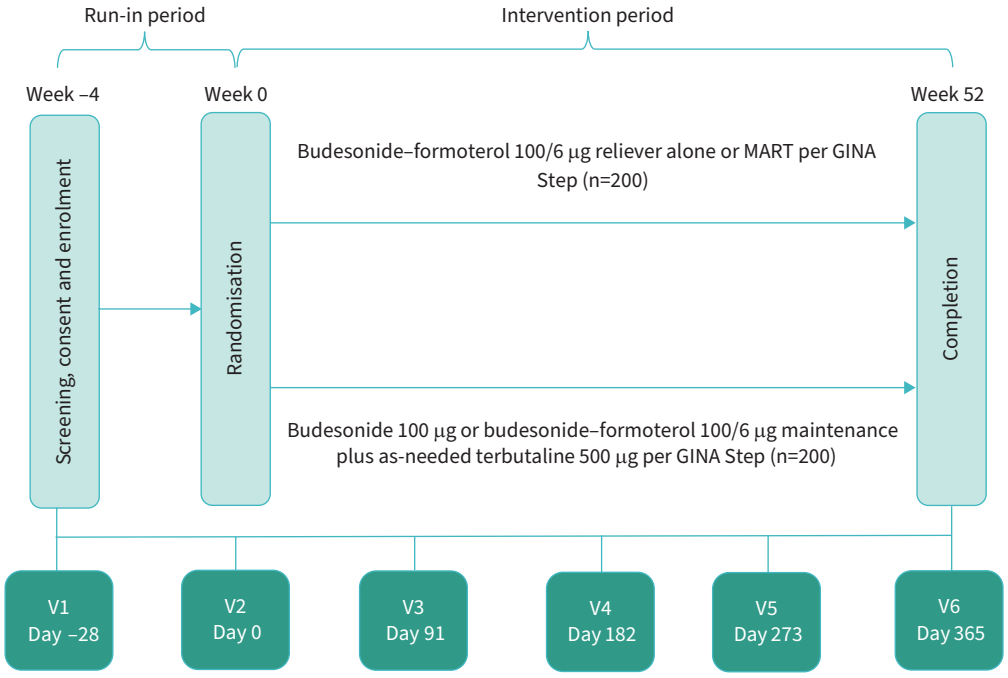

FIGURE 1 Participant timeline. MART: maintenance and reliever therapy; GINA: Global Initiative for Asthma; V: visit.

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 4-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 use a Turbuhaler correctly. Participants will be required to demonstrate an inspiratory flow rate of 30 to 90 $L \cdot min^{-1}$ 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) 100/6 µg dry powder reliever and/or maintenance.
2. Control: budesonide (Pulmicort Turbuhaler, AstraZeneca) 100 µg dry powder inhaler or budesonide–formoterol (Symbicort Turbuhaler, AstraZeneca) 100/6 µg maintenance, with Terbutaline (Bricanyl Turbuhaler, AstraZeneca) 500 µg dry powder inhaler one inhalation as needed.

TABLE 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
Patients of any sex age 5 to 11 years (inclusive) at Visit 1	Already using ICS–formoterol or ICS-salbutamol as a reliever
Doctor diagnosis of asthma (self-report by parent/participant or healthcare provider-reported)	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
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	Any use of systemic corticosteroids in the 6 weeks prior to Visit 1
Registered with a general practitioner	Use of a β-blocker in the 6 months prior to Visit 1
Satisfactory Turbuhaler technique	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)
Inspiratory flow measurement of between 30 and 90 L·min^{-1}	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)
Provision of written informed consent (parent/guardian) and assent (participant)	Any intravenous therapy for the treatment of asthma in the last year
Able and willing to switch from current treatment regimen	Previous intensive care unit admission for asthma, or ventilation for asthma, ever
	Participation in another clinical trial of a medicinal product in the 30 days prior to Visit 1
For randomisation at Visit 2, participants should fulfil the following criteria:	For randomisation at Visit 2, participants are excluded from the study if the following criterion applies:
Satisfactory Turbuhaler technique	Any severe exacerbation, or two moderate exacerbations (per protocol defined criteria) and/or a change in asthma treatment other than run-in study medication from Visit 1 until Visit 2
Inspiratory flow measurement of between 30 and 90 L·min^{-1}	

ICS: inhaled corticosteroid; LABA: long-acting β-agonist; SABA: short-acting β-agonist; GINA: Global Initiative for Asthma.

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 6 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.

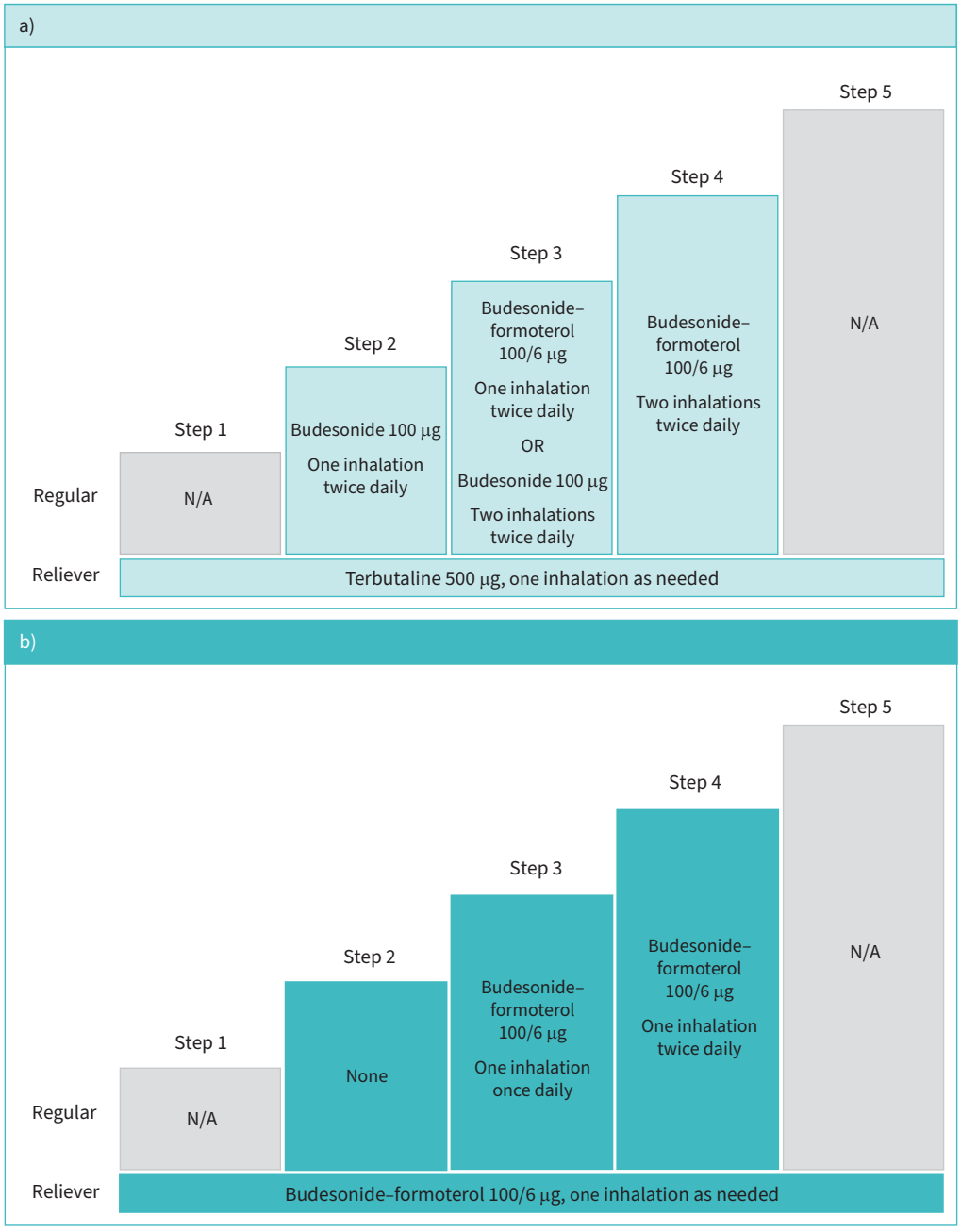

FIGURE 2 START CARE step-wise algorithms. a) Treatment algorithm followed by participants during the run-in period and in the control group. Participants will take budesonide 100 µg (one to two inhalations, twice daily) or budesonide–formoterol 100/6 µg (one to two inhalations, twice daily) maintenance, with terbutaline 500 µg (one inhalation as needed) reliever. Dose determined by Global Initiative for Asthma (GINA) Step at entry. b) Treatment algorithm followed by participants in the intervention group. Participants will take budesonide–formoterol 100/6 µg (one inhalation as needed) reliever at all steps, and at Steps 3 and 4 budesonide–formoterol 100/6 µg (one inhalation, one to two times daily) as maintenance. Dose determined by GINA Step at entry. N/A: not applicable.

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 h.
2. Moderate asthma exacerbation – worsening asthma leading to either: an urgent, unplanned medical review or hospital admission for <24 h, not resulting in an acute prescription of systemic corticosteroids; or the use of systemic corticosteroids for <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, exhaled nitric oxide fraction (F_{ENO}) – 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 1 s (FEV_1) 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 α 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 ⩾1)
- GINA treatment step (Step 2 or >Step 2)

TABLE 2 Objectives and outcome measures

Objectives	Outcome measures	Time point
Primary objective		
To compare the efficacy and safety of budesonide–formoterol maintenance and/or reliever therapy *versus* standard therapy: budesonide maintenance or budesonide–formoterol maintenance, both with terbutaline reliever	Asthma exacerbations (moderate and severe) as a rate per participant per year	52 weeks
Secondary objectives		
To compare the efficacy of budesonide–formoterol maintenance and/or reliever therapy *versus* standard therapy: budesonide maintenance or budesonide–formoterol maintenance, both with terbutaline reliever	Proportion of participants with at least one asthma exacerbation (moderate or severe)	52 weeks
	Proportion of participants with at least one severe exacerbation	52 weeks
	Proportion of participants with at least one step up in treatment	52 weeks
	Proportion of participants on each treatment step	52 weeks
	Severe asthma exacerbations as a rate per participant per year	52 weeks
	Composite of asthma exacerbations (moderate and severe), or step up in treatment as a rate per participant per year	52 weeks
	Proportion of participants with at least one asthma exacerbation (moderate or severe), or step up in treatment	52 weeks
	Step up in treatment, as a rate per participant per year	52 weeks
	Time to first moderate or severe exacerbation	Variable
	Time to first severe asthma exacerbation	Variable
	Time to first exacerbation (moderate or severe), or step up in treatment	Variable
	Time to first step up in treatment	Variable
	F_{ENO}	1, 26 and 52 weeks
	On-treatment FEV_1	1, 26 and 52 weeks
	Days in hospital	52 weeks
	Days lost from school due to asthma	52 weeks
	Days lost from usual activities due to childcare for asthma (parent(s)/guardian(s))	52 weeks
	Asthma Control Questionnaire 5	1, 26 and 52 weeks
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	Total systemic corticosteroid dose	52 weeks
	Change in height from randomisation to study completion	13, 26, 39 and 52 weeks
	Number and proportion of AEs	52 weeks
	Number and proportion of SAEs	52 weeks
	Proportion of participants who discontinue treatment or withdraw	52 weeks
To assess the ability of children to use the Turbuhaler device successfully	Proportion of participants withdrawn due to inability to use the Turbuhaler device	52 weeks
	Number of Turbuhaler retraining events required at each study visit	52 weeks
	Inspiratory flow rate at each study visit	52 weeks
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	Incremental cost per moderate and/or severe exacerbation averted	52 weeks

F_{ENO}: exhaled nitric oxide fraction; FEV_1: forced expiratory volume in 1 s; AEs: adverse events; SAEs: serious adverse events.

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.

TABLE 3 Schedule of trial procedures

	Enrolment/ run-in	Randomisation	Intervention period				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Unscheduled visit
Day	−28	0	91	182	273	365	−28 to 365
Window days	N/A	±14	±7	±7	±7	±7	N/A
Confirm informed consent/assent	X						
Demographics	X						
Inclusion/exclusion criteria	X	X					
Medical history	X						
Asthma history (current treatment and history of severe exacerbations)	X						
Turbuhaler training and assessment of technique	X	X	X	X	X	X	X
Run-in inhalers	d	r					
Randomisation		X					
Height and weight		X	X	X	X	X	
ACQ-5 (IA)		X		X		X	
Health economics data		X	X	X	X	X	X
F_{ENO}[#]		X		X		X	
FEV_1		X		X		X	
Preferences survey[¶]					X		
Dispense trial medication		d	d/r/c	d/r/c	d/r/c	r/c	d/r/c
SAE/AE review		X	X	X	X	X	X
Asthma review (asthma exacerbations and time off school/usual activities)		X	X	X	X	X	X
Asthma action plan and log sheet education and (re-)issue	X	X	X	X	X	X	X
GP communications	X	X				X	X
Dispense/prescribe post-trial medication						X	
Provide parent/participant reimbursement and gift	X	X	X	X	X	X	X

N/A: not applicable; ACQ-5 (IA): Asthma Control Questionnaire, Investigator Administered; F_{ENO}: exhaled nitric oxide fraction; FEV_1: forced expiratory volume in 1 s; SAE: serious adverse event; AE: adverse event; GP: general practitioner; d: dispensed; r: return; c: check. [#]: F_{ENO} must be performed before FEV_1; [¶]: selected sites only.

Data collection

Data will be collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the 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 ⩾2), F_{ENO}, 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 supplementary table S1.

Treatment modification effects (subgroup analyses) will use appropriate interaction terms for the primary outcome variable with estimation of treatment differences within subgroups, 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), F_{ENO} at randomisation, FEV_1 % 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 and spacer.

Data and safety monitoring

Adverse events (AEs) 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 e-mail 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 (SAEs) will be reported to the sponsor within 24 h 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 h 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 SAEs on an expedited basis (within 72 h). They will undertake a formal review of enrolments, withdrawals and AEs every 6 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 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 the 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 end-points 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 100/6 µg 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 100 µg 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 step-wise 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 24 h, and call an ambulance if they use more than eight inhalations. The maximum daily dose of budesonide–formoterol (800/48 µg) was determined based on the relative dose equivalence of repeated doses of formoterol 6 µg with terbutaline 500 µg 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.

Provenance: Submitted article, peer reviewed.

This study is registered at https://anzctr.org.au/ with identifier number ACTRN12622001217796p. Individual participant data that underlie the results reported in this article will be shared, after de-identification (text tables, figures and appendices), 1 year after publication until a minimum of 5 years after publication, with researchers who provide a methodologically sound proposal that has been approved by the START CARE steering committee, to achieve the aims outlined in the approved proposal. Proposals should be directed to M. Holliday (mark.holliday@mrinz.ac.nz). The study protocol, statistical analysis plan, informed consent form and ethical approval are available from https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=384574&isClinicalTrial=False

Ethics statement: Application was made to and approved by Northern B Health and Disability Ethics Committee, New Zealand. Considerations were: this is research in human participants; due to the age of some children informed consent was not possible, children were asked for their assent instead. Privacy: participants were de-identified using a number at enrolment into the study. Human tissues: no tissue samples were taken. Therapeutic medication trial: medications considered safe as approved for use in this age group; however, not in this manner.

Conflict of interest: L. Fleming reports consulting fees from AstraZeneca, Sanofi Regeneron and GSK, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events for AstraZeneca, Novartis and Sanofi Regeneron, outside the submitted work. C.A. Byrnes reports grants or contracts from the National Health and Medical Research Council Australia, Fisher & Paykel, the Buddle Findlay & Paul Stevenson Memorial Fund and FluLab, outside the submitted work; participation on a Clinical Advisory Panel for Cystic Fibrosis New Zealand and as a Bronchiectasis Foundation Trustee, outside the submitted work; and is a group for Chair, Respiratory Network, Paediatric Society of New Zealand, and a member of the Royal Australasian College of Physicians Paediatric Research Committee, outside the submitted work. D. McNamara reports participation on a data safety monitoring board or advisory board for PRECARE study

primary outcome arbitration committee, outside the submitted work; leadership or fiduciary role in other board, society, committee or advocacy group for Co-Chair NZ Paediatric Respiratory and Sleep Clinical Network Reference Group, and Member Scientific Advisory Board, Asthma and Respiratory Foundation of NZ, outside the submitted work. S.R. Dalziel reports grants or contracts from Cure Kids New Zealand, Health Research Council New Zealand and Starship Foundation, outside the submitted work. R. Beasley reports receiving support for the present manuscript from AstraZeneca; grants or contracts from AstraZeneca, Genentech, HRC (NZ) and Cure Kids NZ, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, Avillion, Cipla, Teva and CSL Seqirus, outside the submitted work; support for attending meetings and/or travel from AstraZeneca, Avillion, Cipla, Teva and CSL Seqirus, outside the submitted work; NZ asthma guidelines chair, and GOLD board member, disclosures made outside the submitted work; and receipt of equipment, materials, drugs, medical writing, gifts or other services from AstraZeneca, outside the submitted work. The remaining authors have nothing to disclose.

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