The Children's Anti-inflammatory Reliever (CARE) study: a protocol for a randomised controlled trial of budesonide-formoterol as sole reliever therapy in children with mild asthma

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Shareable abstract (@ERSpublications)
This protocol describes the first randomised controlled trial to investigate the efficacy and safety of budesonide/formoterol as sole reliever therapy for children with mild asthma, providing urgently needed evidence in this population https://bit.ly/35v0R3Z

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Abstract

Background Asthma is the most common chronic disease in children, many of whom are managed solely with a short-acting β_2-agonist (SABA). In adults, the evidence that budesonide-formoterol as sole reliever therapy markedly reduces the risk of severe exacerbations compared with SABA alone has contributed to the Global Initiative for Asthma recommending against SABA monotherapy in this population. The current lack of evidence in children means it is unknown whether these findings are also relevant to this demographic. High-quality randomised controlled trials (RCTs) are needed.

Objective The aim of this study is to determine the efficacy and safety of as-needed budesonide-formoterol therapy compared with as-needed salbutamol in children aged 5 to 15 years with mild asthma, who only use a SABA.

Methods A 52-week, open-label, parallel group, phase III RCT will recruit 380 children aged 5 to 15 years with mild asthma. Participants will be randomised 1:1 to either budesonide-formoterol (Symbicort Rapihaler®) 50/3 µg, two actuations as needed, or salbutamol (Ventolin®) 100 µg, two actuations as needed. The primary outcome is asthma attacks as rate per participant per year. Secondary outcomes assess asthma control, lung function, exhaled nitric oxide and treatment step change. A cost-effectiveness analysis is also planned.

Conclusion This is the first RCT to assess the safety and efficacy of as-needed budesonide-formoterol in children with mild asthma. The results will provide a much-needed evidence base for the treatment of mild asthma in children.

Introduction

Background and rationale

Asthma is the most common chronic condition in children worldwide [1]. Many are deemed to have mild or intermittent disease and are managed with short-acting β_2-agonist (SABA) reliever therapy alone [2, 3]. Whilst SABAs provide rapid symptom relief, they do not treat the underlying airway inflammation that is often present even in children with infrequent symptoms [4]. Inhaled corticosteroids (ICS) represent the mainstay of anti-inflammatory therapy in asthma, with relatively small daily doses achieving significant reductions in symptom burden and asthma attacks [5, 6]. Current international guidelines recommend regular use of ICS for children with asthma symptoms on two or more occasions per month [7]. However, ICS are often under-prescribed by clinicians and under-utilised by patients, due in part to overestimation of asthma control and steroid-aversion [8]. This renders many patients who should be on ICS therapy overly dependent on SABA, increasing their risk of morbidity and mortality [9].

In adults and adolescents with mild and mild-to-moderate disease, the combination of the ICS budesonide with formoterol, a fast-onset long-acting β_2-agonist (LABA), in a single inhaler taken as needed has been shown to significantly mitigate the risk of severe asthma attacks [10–13]. This regimen results in a 57% reduction in severe attacks in adults and adolescents compared with SABA-only treatment (relative effect 0.43, 95% credible interval 0.33 to 0.72) [14]. A *post hoc* analysis of participants aged 12 to 17 years enrolled in the SYmbicort Given as needed in Mild Asthma (SYGMA) 1 trial reported a reduction in severe exacerbations of 77% in this population (rate ratio 0.23, 95% confidence interval (CI) 0.09 to 0.65) [15], suggesting at least similar efficacy of as-needed ICS-formoterol therapy in children.

A 15% reduction in severe attacks was also observed compared with maintenance ICS plus as-needed SABA in adults and adolescents (rate ratio 0.85, 95% CI 0.72 to 1.00, p=0.044) [16]. In another *post hoc* analysis of the SYGMA 1 trial, even a single day of increased budesonide-formoterol use in adults and adolescents demonstrated protection against a severe attack equivalent to that achieved with maintenance ICS [17].

The findings of these four randomised controlled trials (RCTs) [10–13] contributed to two significant changes in asthma management. Firstly, the Global Initiative for Asthma (GINA) stopped recommending SABA monotherapy for adults and adolescents with asthma [18]. Secondly, the extension of evidence for ICS-formoterol from Maintenance And Reliever Therapy (MART) in moderate and severe asthma [19] to include as-needed therapy in mild asthma gave rise to the Anti-Inflammatory Reliever (AIR) concept, in which ICS-formoterol is used as a reliever, with or without maintenance ICS-formoterol, across the spectrum of asthma severity [20, 21]. This approach makes it possible for most patients to be managed with a single ICS-formoterol combination inhaler, with the maintenance dose determined by baseline asthma severity, and the frequency of reliever use titrated in response to symptoms.

Whether the findings relating to ICS-formoterol reliever therapy alone in mild asthma are relevant to children under the age of 12 years is unknown as no such RCTs have been undertaken in this age group. However, in children aged 4 to 11 years with moderate to severe asthma, budesonide-formoterol MART reduced the risk of severe asthma attacks compared to maintenance budesonide-formoterol plus terbutaline (risk ratio 0.34, 95% CI 0.19 to 0.60) [22]. Importantly, this risk reduction was greater in magnitude than in participants aged 12 to 80 years in the same study [23], again suggesting potentially greater efficacy of the AIR component in this younger population [24].

We hypothesise that as-needed budesonide-formoterol will have greater efficacy and a favourable safety profile compared with salbutamol reliever therapy in children aged 5 to 15 years.

Objective

The primary objective is to determine the efficacy and safety of as-needed budesonide-formoterol therapy compared with as-needed salbutamol in children aged 5 to 15 years with mild asthma who only use a SABA reliever.

Methods

Study design

The Children's Anti-inflammatory Reliever (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). It is funded by project grants from the Health Research Council of New Zealand and Cure Kids and has undergone full external peer review as part of this funding process.

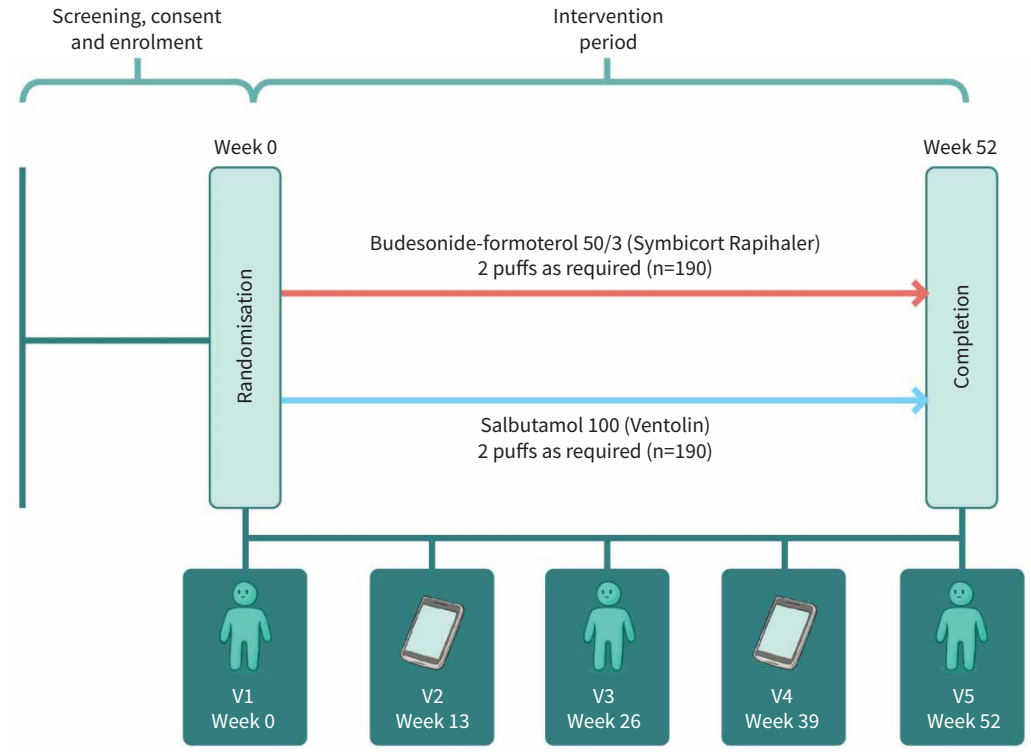

FIGURE 1 Participant timeline.

This research is conducted with support from AstraZeneca Ltd., Auckland, New Zealand, by supply of the Symbicort Rapihaler medication only. AstraZeneca has no role in trial design; the collection, analysis and interpretation of data; the writing of the protocol; or the decision to submit manuscripts for publication.

The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12620001091998). It was approved by the Northern B Health and Disability Ethics Committee (20/NTB/200). Regulatory approval for the use of Symbicort Rapihaler 50/3 µg in New Zealand was granted by the Standing Committee on Therapeutic Trials (20/SCOTT/98).

Participants and recruitment

A total of 380 participants aged 5 to 15 years with asthma (diagnosed by any doctor), only using a SABA reliever, will be recruited at clinical trial sites and primary care-based research centers. Participants will be identified from clinical trial unit databases, general practices, emergency departments, 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 are required prior to enrolment. Participants who turn 16 years of age during the study will be required to provide informed consent at their next in-person visit.

Interventions

Eligible participants will be randomised 1:1 to receive as needed for relief of asthma symptoms:

1. Intervention: Budesonide-formoterol 50/3 µg pressurised metered-dose inhaler (Symbicort Rapihaler®, AstraZeneca) two actuations *via* spacer (Space Chamber Plus®, Medical Developments International Ltd., Victoria, Australia).
2. Control: Salbutamol 100 µg pressurised metered-dose inhaler (Ventolin®, GlaxoSmithKline, Brentford, UK) two actuations *via* spacer (Space Chamber Plus®, Medical Developments International Ltd).

Investigators will escalate treatment following a severe asthma attack, using treatment arm-specific stepwise algorithms (figure 2). In line with current New Zealand asthma guidelines [25, 26], participants on

TABLE 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
Aged 5 to 15 years	Hospital admission (⩾24 h) for asthma in the last 12 months
Doctor diagnosis of asthma (parent/participant or doctor-reported) *AND*	Self-reported use of >6 SABA inhalers in the last 12 months (*i.e.* poor-control)
SABA use on three or more consecutive days in the last 12 months, *AND/OR*	Any use of ICS, LABA, LTRA, theophylline, anticholinergic agent or cromone in the last 6 months
SABA use on two or more days per month, on average, in the last 12 months, *AND/OR*	Any use of systemic corticosteroids in the last 6 weeks
Urgent medical review for worsening asthma in the last 12 months	Any medical condition which, at the Investigator's discretion, may present a safety risk or impact the feasibility of the study or the study results (including, but not limited to, other significant respiratory comorbidities, such as cystic fibrosis and bronchiectasis)
Registered with a General Practitioner	Any known or suspected contraindications to the medications prescribed in the study or their respective excipients
	Previous life-threatening asthma (intensive care unit admission)
	Unable or unwilling to switch from current asthma treatment regimen
	Unable or unwilling to provide written informed consent (parent(s)/guardian(s)) or assent/consent (participant)
	Self-reported current pregnancy or breastfeeding at the time of enrolment

SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist.

salbutamol only will add maintenance low-dose fluticasone (Flixotide®, GlaxoSmithKline) at step 2; this will be replaced by maintenance low-dose fluticasone-salmeterol (Seretide®, GlaxoSmithKline) at step 3 if a further severe asthma attack occurs. Participants receiving budesonide-formoterol will be escalated using a paediatric-dose-adjusted AIR regimen, transitioning from budesonide-formoterol as needed to MART, very-low-dose at step 2 and, if a further severe asthma attack occurs, low-dose at step 3. This is in line with the proposed children's [27] and adult's [20, 21] AIR therapy algorithms.

The participant's usual healthcare provider may increase their treatment for other reasons, including poor asthma symptom control. In these instances, the Investigator will maintain the upregulation of treatment but ensure that it is in keeping with the randomised study treatment algorithms.

Outcome measures

The primary outcome is asthma attacks as rate per participant per year. An "asthma attack" encompasses both moderate and severe attacks, in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations [28]:

1. Moderate asthma attack: Worsening asthma leading to an urgent, unplanned medical review (*e.g.* primary care or emergency department visit) or hospital admission; not resulting in the prescription of systemic corticosteroids (tablets, suspension or injection).
2. Severe asthma attack: Worsening asthma leading to an urgent, unplanned medical review (*e.g.* primary care or emergency department visit) or hospital admission; resulting in the prescription of systemic corticosteroids.

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

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

Secondary outcome measures (table 2) have been chosen to provide clinically relevant information on the efficacy and safety of the randomised treatments. A cost-effectiveness analysis is also planned.

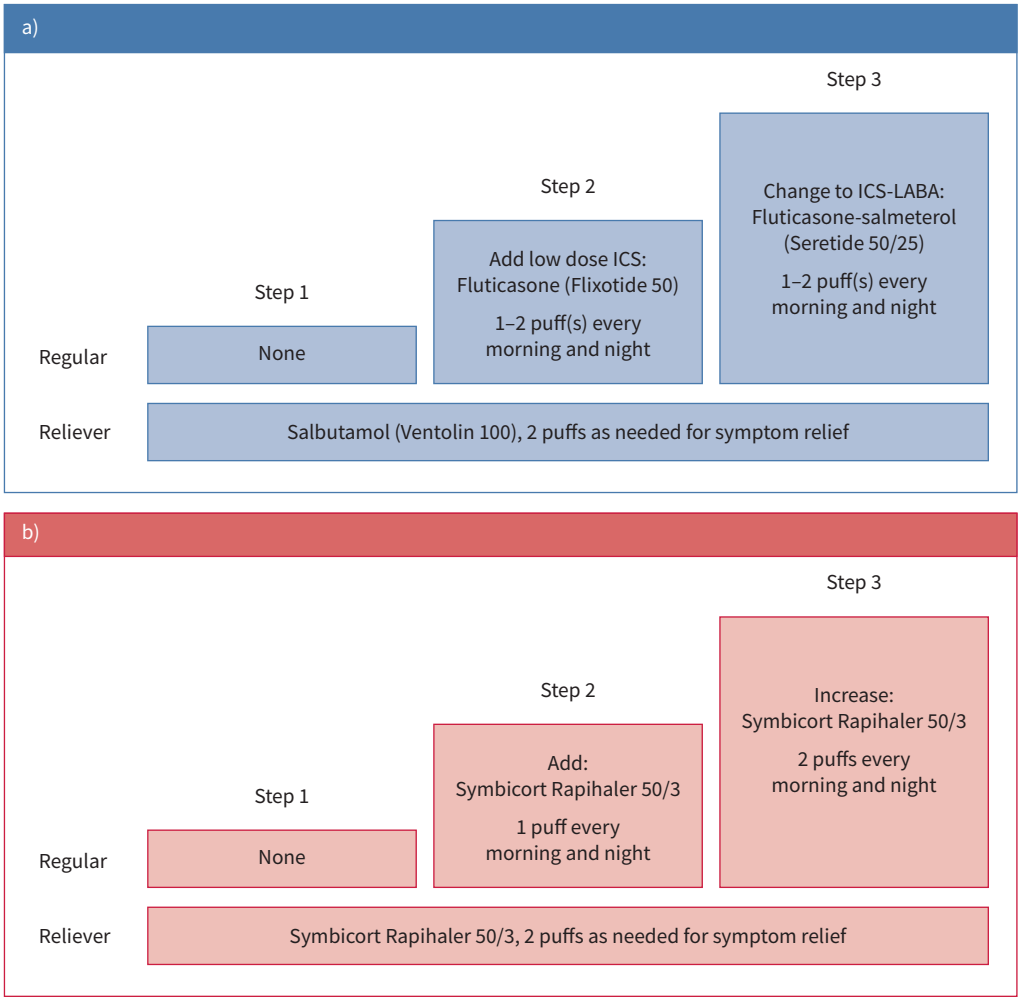

FIGURE 2 CARE stepwise algorithms. a) Treatment algorithm followed by participants in the control group. Daily doses are aged-adjusted; participants aged 5 to 11 years will take 100 µg of fluticasone daily (one puff, twice daily), whereas participants aged ⩾12 years will take 200 µg (two puffs, twice daily). Fluticasone will be administered alone (Step 1) or in combination with salmeterol (Step 3). b) Paediatric-dose-adjusted Anti-Inflammatory Reliever (AIR) algorithm followed by participants in the intervention group. Participants will take 100 µg of budesonide daily (one puff, twice daily) at Step 2, and 200 µg of budesonide daily (two puffs, twice daily) at Step 3. ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist.

Trial procedures

Participants will attend a total of five study visits over the 52-week study period (figure 1; table 3). Visits 1, 3 and 5 will be conducted in-person at a trial site; visits 2 and 4 will be conducted *via* telephone.

An overview of the study procedures is provided in table 3. Asthma control will be assessed using the Asthma Control Questionnaire (ACQ-5; symptoms-only version) at visits 1, 3 and 5. The interviewer-administered version will be used for participants aged 10 years and younger on study entry. At visits 1 and 5, fractional exhaled nitric oxide (F_{eNO}) – a biomarker of Type 2 inflammation – will be measured in accordance with ATS guidelines [29], using a FeNOBreath® device (Bedfont Scientific, Maidstone, UK). On-treatment forced expiratory volume in 1 s (FEV_1) will be measured 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 [30], using Global Lung Function Initiative (GLI) reference ranges [31].

Participants will be issued with study inhalers at each visit (these will be couriered to the participant for visits 2 and 4). 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 as required during the

TABLE 2 Objectives and outcome measures

Objectives	Outcome measures	Time point
Primary objective		
To determine the efficacy and safety of as-needed budesonide-formoterol compared with salbutamol reliever therapy	1. Asthma attacks as rate per participant per year	52 weeks
Secondary objectives		
To determine the **efficacy** of as-needed budesonide-formoterol compared with salbutamol	2. Severe asthma attacks as rate per participant per year	52 weeks
	3. Proportion of participants with at least one asthma attack	52 weeks
	4. Proportion of participants with at least one severe asthma attack	52 weeks
	5. Proportion of participants on each treatment step	52 weeks
	6. Time to first asthma attack	Variable
	7. Time to first severe asthma attack	Variable
	8. Days in hospital (due to asthma)	52 weeks
	9. Fractional exhaled nitric oxide (F_{eNO})	52 weeks
	10. On-treatment forced expiratory volume in 1 s (FEV_1)	52 weeks
	11. Asthma Control Questionnaire 5 (ACQ-5)	26 and 52 weeks
	12. Days lost from school due to asthma	52 weeks
	13. Days lost from work due to asthma (participant)	52 weeks
	14. Days lost from work due to childcare for asthma (parent(s)/guardian(s))	52 weeks
To determine the **safety** of as-needed budesonide-formoterol compared with salbutamol	15. Total systemic corticosteroid dose	52 weeks
	16. Growth velocity	52 weeks
	17. Adverse events	52 weeks
	18. Serious adverse events	52 weeks
To determine the **cost-effectiveness** of as-needed budesonide-formoterol compared with salbutamol	19. Net cost per asthma attack prevented	52 weeks

study. 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 asthma action plans [32]. 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 asthma attack, the need for additional study medication and consideration of withdrawal.

Following study completion, participants will be provided with post-trial treatment in alignment with the New Zealand asthma guidelines at the time. 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 attack rates between 0.51 in the salbutamol arm and 0.28 in the budesonide-formoterol arm (a relative rate 0.55) with 90% power and two-sided α of 5%. Assuming a dropout rate of 20%, a total of 380 participants (190 in each arm) will be recruited.

A masked assessment of the rate of asthma attacks in the two arms is planned after 60% (n=228) of participants have been recruited. We will estimate a 95% confidence interval for the highest rate of asthma attacks and use this as the basis of a re-estimation for the sample size. This will still be based on detecting a relative rate of 0.55, using the upper and lower 95% confidence limits for the highest rate as the basis for the re-estimation. The number of participants recruited will be adjusted accordingly, resources permitting.

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 previous 12 months (0 or $\geqslant$1)
- Age group (5 to 11 years; 12 to 15 years)

TABLE 3 Schedule of trial procedures

Visit number	Consent/ enrolment	1	2	3	4	5	Unscheduled visit
Week	0	0	13	26	39	52	A/R
Day	0	0	91	182	273	365	A/R
Visit window days	N/A	N/A	±7	±7	±7	±7	N/A
Confirm informed consent/assent	X[#]	X[¶]	X	X	X	X	
Inclusion/exclusion criteria check	X[#]	X[¶]					
Medical history and demographics	X[#]	X[¶]					
Asthma review (including review of MyCap and paper logbook): (i) Asthma attacks (ii) AEs (iii) SAEs (iv) Medication changes (including use of additional medication) (v) Days lost from school due to asthma (vi) Days lost from work due to asthma (participant) or for childcare due to asthma (parent(s)/guardian(s))			X	X	X	X	A/R
Height and weight		X				X	
Randomisation		X					
ACQ-5		X		X		X	
F_{eNO}[+]		X				X	
Health economics questionnaires		X		X		X	
On-treatment FEV_1		X				X	
Inhaler technique assessment		X		X		X	A/R
Inhaler technique education		X		X		X	A/R
Issue written information including action plan and MyCap		X		X		X	A/R
Dispense trial medication (randomised regimen)		X		X			A/R
Courier trial medication to participant and confirm receipt			X		X		
Dispense post-trial medication						X	
Inform GP of study enrolment		X					
If participant is to be withdrawn, documentation of cause and notification to GP and Sponsor						X	
Inform GP and Sponsor of study completion						X	
Provide reimbursement for expenses		X		X		X	X
Provide participant gift				X			
Provide badge (V1) and certificate (V5)		X				X	

A/R: as required; N/A: not applicable; AE: adverse event; SAE: serious adverse event; ACQ-5: Asthma Control Questionnaire, five question (symptom-only) version; F_{eNO}: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 s; GP: general practitioner. [#]: perform at enrolment visit if enrolment visit and Visit 1 to be done on different days. [¶]: re-confirm at Visit 1 if enrolment visit on different day. [+]: F_{eNO} must be performed prior to spirometry.

Where two or more participants in the same primary household are currently enrolled in the study, the first participant will be randomised as above; all subsequent participants in the same primary household will be allocated to receive the same treatment as the first participant. This is to improve compliance with the treatment regimens.

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 REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the Medical Research Institute of New Zealand (MRINZ) [33, 34]. A

REDCap-based Clinical Data Management Application (CDMA) will facilitate the electronic collection of data in real time during clinic visits. Data will also be collected *via* MyCap (a mobile application extension of REDCap), participant logs, and through participant and/or parent/guardian-report at each visit.

Statistical methods

The statistical analysis will be by intention to treat, performed by the study statistician masked as to treatment allocation. SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) will be used.

The analysis of the primary outcome variable, the count of asthma attacks in relation to the time of observation in the study, will be by estimation of the relative rate of total asthma attacks 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: age, sex, ethnicity, baseline ACQ-5 score, and the number of severe asthma attacks in the previous year, to account for different distributions of these variables in the treatment groups and to increase precision of the estimates of differences. For illustrative purposes age will also be considered as a dichotomous variable split by age group (5 to 11 years; and 12 to 15 years).

An overview of the methods used to analyse secondary outcome measures is given in table 4.

Cost-effectiveness analysis

A baseline cost-effectiveness analysis will be undertaken that, for each treatment, calculates the net cost per attack event that is prevented. Net costs will include direct treatment costs (*e.g.* medication, staff time and time costs for self-administered medication) as well as cost averted (*e.g.* fewer days off school, and savings in childcare costs for sick children). An extension of the cost-effectiveness analysis is to add consideration of benefits such as reduced distress from attacks and reduced anxiety (for the child and parent(s)/guardian(s)) as severe events are reduced. The addition of factors such as savings in distress will be used to transform the analysis into a full cost-benefit (or cost-utility) analysis, which forms a more appropriate guide for public policy decision-making.

Data and safety monitoring

An independent Data and Safety Monitoring Committee (DSMC) has been established, with membership comprising a biostatistician and clinicians with paediatric and research experience. A masked interim safety assessment for all unplanned hospital admissions of ⩾24 h duration for asthma will take place after 60% (n=228) of participants have been recruited. If there are ⩾20 events, a masked analysis will be performed. The DSMC will review the results of this analysis. If the findings of the analysis indicate a safety review is necessary, then termination of the trial will be considered.

Discussion

This study is the first RCT of ICS-formoterol as sole reliever therapy in children aged 5 to 15 years. Data in this age group is urgently needed to determine if the substantial benefits observed in the SYGMA 1 [12] and Novel Symbicort Turbuhaler Asthma Reliever Therapy (Novel START) [10] RCTs are also relevant to this population; if a similar reduction in asthma attacks is demonstrated, it has the potential to markedly improve asthma outcomes in children globally.

The primary outcome of asthma attacks as rate per participant per year was chosen as asthma attack prevention is a key tenet of asthma management, with rate the preferred measure in clinical trials [28]. Determining asthma attack severity is in part subjective. In recognition of this, prescription of oral corticosteroids for worsening asthma was pragmatically determined to constitute a severe asthma attack and is a consistent element used in definitions of asthma attacks in other paediatric studies [22, 35, 36]. This respects the prescribing clinician's judgement of severity.

The age cut-off of 15 years was in keeping with the New Zealand child asthma guidelines at the time of study development [37] and aligns with the 2021 European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children [38]. The SYGMA trials [12, 13] included participants aged 12 years and older, providing some data for adolescents [15]. However, there have been no open-label trials to include this lower age group. This study will also differ by using pressurised metered-dose inhalers (pMDIs) rather than dry powder inhalers and a different dose of budesonide-formoterol (50/3 µg per actuation *versus* 200/6 µg).

TABLE 4 Secondary outcome variable analyses

Method of analysis	Secondary outcome variables
Poisson regression with an offset for the time of observation and a fixed effect of randomised treatment allocation	Severe asthma attacks per participant per year Number of days lost from school due to asthma Number of days lost from work due to asthma (participant) Number of days lost from work 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 attack The proportion of participants with at least one severe asthma attack The proportion of participants on each treatment step[¶] 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 attack Time to first severe asthma attack
ANCOVA with baseline (where taken) as a continuous covariate	FEV_1 FEV_1 z-score FEV_1 % predicted FEV_1 prediction value (GLI values) F_{eNO} (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 oral corticosteroid dose[+]
Descriptive data	Total ICS dose (for inhalers with dose counters)

FEV_1: forced expiratory volume in 1 s; GLI: Global Lung Function Initiative; F_{eNO}: fractional exhaled nitric oxide; ACQ-5: Asthma Control Questionnaire; ICS: inhaled corticosteroid. All estimates will be given as 95% confidence intervals, and so with a nominal two-sided Type I error rate of 5%. We will not adjust secondary analyses for multiple analyses and so the secondary analyses will be considered exploratory. [#]: 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 descriptively. [¶]: data for the proportion of participants on each treatment step is likely to be sparse. We will consider merging data for treatment steps 2 and 3. If it is not possible or appropriate to use logistic regression, the data will be analysed descriptively. [+]: data for oral steroid use is likely to be sparse. Methods that will be explored include: dichotomous variable "had a 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.

Blinding was impractical for a number of reasons. Firstly, the inhalers used in the study are visually different and the costs associated with standardising these are prohibitive. Secondly, using placebo inhalers in each arm (*i.e.* placebo Symbicort Rapihaler-shaped inhaler in the SABA arm, and vice versa) would require participants to take four puffs each time for symptom relief (two puffs from each inhaler), increasing participant burden, decreasing adherence and not representing real-world care. Thirdly, all participants who have a severe asthma attack will have their treatment stepped up (protocol-driven) to ensure their safety. SABA-only participants will add on separate inhalers (ICS or ICS-LABA) as per current guideline recommendations, whereas participants on budesonide-formoterol will be stepped up to budesonide-formoterol MART (single inhaler). The different inhalers prescribed in the two regimens would therefore present a significant challenge to ongoing blinding and would not maintain the real-world advantage of using a single combination inhaler in the intervention arm. Fourthly, the open-label design enables basic exploration of a paediatric AIR stepwise treatment regimen, which would be difficult if blinded, owing to the reasons outlined above.

Particular consideration was given to reducing unnecessary ICS exposure in the intervention arm. Participants in the four adult studies of ICS-formoterol all used Symbicort Turbuhaler (budesonide/formoterol) 200/6 µg, one actuation as needed [10–13]. This approach was deemed less suitable for children due to the relatively high steroid dose per actuation, as well as the difficulties in coordinating actuations with a Turbuhaler in the younger age group [25]. The use of Symbicort Rapihaler 50/3 µg, two actuations as needed with a spacer device, delivers half the steroid dose per use episode, as per current guideline recommendations [7, 25], and is in keeping with other paediatric studies of as-needed ICS [35, 36]. Using a 50/3 µg preparation rather than a 100/6 µg also helps to prevent excess ICS exposure resulting from the ingrained behaviour of taking two actuations per use episode. Keeping the dose the same for all children facilitates evaluation of whether the reduction in asthma attacks observed in 12- to 15-year-olds in SYMGA 1 [12] can be achieved with lower ICS doses.

All participants are issued with asthma action plans, modified from the New Zealand asthma action plans. Participants in both arms are recommended to seek medical help the same day if they use 12 or more actuations in 24 h, and to call for an ambulance if they have used 16 or more. The maximum recommended daily dose of budesonide-formoterol (800/48 µg) was determined based on the relative dose equivalence of formoterol 6 µg with salbutamol 200 µg [39–41], available regulatory safety datasheets, and the results of MART in children [21].

In conclusion, this Investigator-initiated and independently funded RCT will be the first to compare the efficacy and safety of as-needed budesonide-formoterol with as-needed salbutamol in children with mild asthma, providing data on asthma attack prevention, symptom control, exhaled nitric oxide, lung function, steroid-related side-effects and cost-effectiveness.

This study is registered at www.anzctr.org.au with identifier number ACTRN12620001091998. Individual participant data for this trial (including data dictionaries) will be made available, upon request, one year after publication until a minimum of 5 years after publication. Researchers must provide a methodologically sound proposal for consideration by the CARE steering committee.

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