An open-label Randomised Controlled Trial of as-needed budesonide-formoterol vs salbutamol reliever therapy in mild childhood asthma

PROTOCOL

Short title	Children's Anti-inflammatory REliever (CARE)
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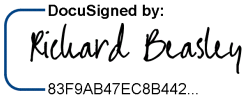
Chief Investigator signature



Confidentiality statement This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Funder, the Investigator Team and members of the Research Ethics Committee, unless authorised to do so.

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3 SYNOPSIS

Trial Title:	An open-label Randomised Controlled Trial of as-needed budesonide-formoterol vs salbutamol reliever therapy in mild childhood asthma
Short Title:	Children's Anti-inflammatory REliever (CARE)
Clinical Phase:	Phase III
Trial Design:	A multi-centre, open-label, parallel group, randomised controlled trial (RCT)
Trial Participants:	Children aged five to 15 years with mild asthma currently taking short-acting beta$_2$-agonist (SABA) reliever therapy only
Planned Sample size:	360
Trial sites:	Participants will be recruited from sites throughout NZ
Trial Period:	Recruitment: 52 weeks Treatment duration: 52 weeks Follow-up (post-trial) duration: Nil
Intervention arm regimen:	Budesonide-formoterol 50/3mcg metered dose inhaler (Symbicort Rapihaler) two actuations via spacer (Airflow Space Chamber Plus) as needed for relief of asthma symptoms
Control arm regimen:	Salbutamol 100mcg metered dose inhaler (Ventolin) two actuations via spacer (Airflow Space Chamber Plus) as needed for relief of asthma symptoms
Trial hypothesis:	The use of as-needed budesonide-formoterol has greater efficacy and a favourable safety profile compared with salbutamol reliever therapy
Primary objective:	To determine the efficacy and safety of budesonide-formoterol reliever therapy compared with salbutamol reliever therapy
Primary outcome:	1. Asthma attacks as rate per participant per year
Secondary outcomes:	2. Severe asthma attacks as rate per participant per year 3. Time to first asthma attack 4. Time to first severe asthma attack 5. Proportion of participants with at least one asthma attack 6. Proportion of participants with at least one severe asthma attack 7. Proportion of participants on each treatment step 8. Days in hospital 9. FeNO at 52 weeks 10. On-treatment FEV1 at 52 weeks 11. ACQ-5 at 26 and 52 weeks 12. Days lost from school due to asthma 13. Days lost from work due to asthma (participant) 14. Days lost from work due to childcare for asthma (parent(s)/ guardian(s)) 15. Total systemic corticosteroid dose 16. Growth velocity 17. Adverse Events (AEs) 18. Serious Adverse Events (SAEs) 19. Cost effectiveness as net cost per attack event that is prevented
Nested sub-study	CAREtoon (separate protocol)
Statistical analysis:	Intention-to-treat by a biostatistician masked to treatment allocation

4 ABBREVIATIONS AND DEFINITIONS

4.1 Abbreviations

ACQ-5	Asthma Control Questionnaire
ADL	Activities of Daily Living
AE	Adverse Event
AR	Adverse Reaction
AZ	AstraZeneca
ATS	American Thoracic Society
CI	Confidence Interval
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic case report form
ED	Emergency Department
ERS	European Respiratory Society
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume over 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GP	General Practitioner
GSK	GlaxoSmithKline
HDEC	Health and Disability Ethics Committee
HRC	Health Research Council of New Zealand
IB	Investigator Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
IMP	Investigational Medicinal Product
LABA	Long-Acting $Beta_2$-Agonist
LTRA	Leukotriene Receptor Antagonist
MART	Maintenance and Reliever Therapy
MRINZ	Medical Research Institute of New Zealand
NZ	New Zealand
PI	Principal Investigator
PIS	Participant Information Sheet
PIS-CF	Participant Information Sheet-Consent Form
PIS-AF	Participant Information Sheet-Assent Form
pMDI	pressurised Metered-Dose Inhaler
REDCap	Research Electronic Data Capture
RCT	Randomised Controlled Trial
SABA	Short-Acting $Beta_2$-Agonist
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom

4.2 Definitions

Asthma attack: A moderate asthma attack is defined as:

- Worsening asthma leading to an urgent, unplanned medical review (e.g. primary care or emergency department (ED) visit) or hospital admission; **not** resulting in the prescription of systemic corticosteroids (tablets, suspension, or injection – e.g. oral prednisone).

A severe asthma attack is defined as:

- Worsening asthma leading to an urgent, unplanned medical review (e.g. primary care or ED visit) or hospital admission; resulting in the prescription of systemic corticosteroids (tablets, suspension, or injection – e.g. oral prednisone).

An "asthma attack" encompasses both moderate and severe asthma attacks. Note, for an 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.[1]

Participant Refers to the child enrolled in the study.

24-hour period: From midnight to midnight, at local time to the investigator site.

Study visits: A scheduled study visit refers to any of the pre-specified study participant consultations.

An unscheduled study visit refers to any visit arranged in addition to the scheduled consultations and takes place outside of scheduled visit windows.

End of trial: The end of trial is the date of the last visit of the last participant.

5 BACKGROUND AND RATIONALE

5.1 The burden of asthma

New Zealand has one of the highest rates of childhood asthma in the world, with one in seven children affected. The impact is significant; childhood asthma accounts for 4.4 days off school, up to 10% of all NZ general practitioner (GP) consultations for children, over 325,000 asthma-related prescriptions, and more than 3000 hospital admissions, every year.[2–8]

Over half of children with asthma worldwide are considered to have mild disease, treated with SABA alone.[9–14] In NZ, 28,000 children with asthma aged six to 12 years are managed solely with SABA (PHARMAC data). However, there are a number of safety concerns with SABA monotherapy, which contribute to poor asthma control and increased attack risk in this group:

- The lack of activity against the underlying inflammatory processes in asthma, present even in mild disease;[14–16]
- The potential to increase bronchial hyper-responsiveness thereby increasing asthma severity;

- Delays to the introduction of inhaled corticosteroid (ICS) therapy, resulting in reduced efficacy;[17]
- Overreliance on SABAs, leading to entrenched behaviour of as-needed inhaler use, contrary to that required with regular maintenance therapy;[17]
- The paradox of banning long-acting beta$_2$-agonist (LABA) monotherapy but not SABA monotherapy despite evidence that both have serious risks when used as monotherapy;[18]
- Overuse during an attack leading to delay in seeking medical review, thereby increasing mortality risk. [17,18]

Improved asthma control can be achieved by the addition of maintenance low-dose ICS.[19,20] The inhaled Steroid Treatment As Regular Therapy (START) study, an RCT of early ICS versus placebo in 7,138 children and adults with mild asthma, found that the cumulative risk of having at least one severe attack during the full five years of the study was 39% lower in the maintenance ICS group.[21] These benefits were seen in participants experiencing symptoms less than one day per week, reiterating the value of ICS even in people with mild disease.[22]

The benefits of ICS are restricted in clinical practice by the overestimation of asthma control and, in some cases, steroid aversion.[23–26] This leads to the under prescribing of ICS by clinicians, and reduced adherence to ICS by patients. As a result, many children who should be on regular ICS therapy are not, rendering them overly reliant on SABAs as their sole asthma treatment.

Concerns about the impact on growth of regular ICS use in children further negatively affect adherence. The Childhood Asthma Management Programme (CAMP) found that regular low-dose ICS use resulted in a small reduction in adult height (adjusted mean -1.2 cm, 95% CI -1.9 to -0.5).[27] The impact of ICS on growth can be minimised by prescribing the lowest dose of ICS required to maintain good asthma control.[28] Importantly, poorly controlled asthma can also result in poor growth.[28,29]

5.2 Alternatives to SABA monotherapy (evidence from paediatric studies)

As-needed ICS and SABA (separate inhalers): The TReating children to prevent EXacerbations of Asthma (TREXA) study demonstrated that the risk of a first attack in children with mild asthma taking regular ICS was reduced by half (hazard ratio (HR) 0.49, 95% confidence interval (CI) 0.28 to 0.85) compared to those stepped down to SABA only therapy, in accordance with guidelines.[30] The risk of a first attack was reduced by a third (HR 0.62, 95% CI 0.37 to 1.05) in those taking as-needed ICS with SABA, compared to SABA alone, although this result was not statistically significant. These findings illustrate the potential harms of SABA monotherapy and the clear need for ICS even in children who would traditionally be ‘stepped down’ to SABA only treatment. There was no significant difference in linear growth for children taking ICS as-needed compared to SABA alone (p=0.26), whereas children taking daily ICS grew 1.1cm (SD 0.3) less (p<0.0001).

The Asthma Symptom-based Inhaled STeroid (ASIST) study compared regular ICS plus as-needed SABA versus as-needed ICS and SABA therapy in African-American children with mild asthma already taking ICS.[31] The proportion of children who had an asthma attack, and the time to first attack, were not significantly different between the two treatments despite those prescribed as-needed ICS using a much lower dose (526 vs. 1,961 mcg per month). Both parents and paediatricians favoured as-needed ICS with SABA.[31,32] ICS with SABA taken as needed can be considered an alternative management strategy to daily ICS plus SABA reliever for mild asthma, and may be acceptable to children and their parents/guardians. The clinical potential of these results is limited by the use of separate inhalers rather than one combination inhaler, which has not been trialled in children.

ICS-LABA Maintenance And Reliever Therapy (MART): In children aged four to 11 years with moderate to severe asthma, budesonide-formoterol MART reduced the risk of asthma attacks (risk ratio 0.43, 95% CI 0.21 to 0.87), and had less of an impact on growth (mean difference 1cm, 95% CI 0.3 to 1.7cm) compared to maintenance high-dose budesonide plus as-needed terbutaline.[33–35] Importantly, MART reduced the risk of severe attacks compared with regular ICS-formoterol plus terbutaline reliever

therapy to a greater extent than that observed in adults and adolescents (risk ratio 0.28, 95% CI 0.14 to 0.53 vs. 0.59, 95% CI 0.49 to 0.71, respectively).[36,37]

5.3 Alternatives to SABA monotherapy (evidence from adult studies)

As-needed ICS-SABA (combination therapy): One study has examined the efficacy of a symptom-driven ICS-SABA combination inhaler in adults with mild asthma.[38] As-needed ICS-SABA was as effective as regular ICS plus SABA reliever therapy, and superior to SABA reliever therapy, at controlling asthma symptoms and reducing attack risk. This benefit was achieved using a lower total dose of ICS than with regular ICS (18.5 vs. 77.0mg). The generalisability of these results is hindered by limited access to ICS-SABA combinations.

As-needed ICS-LABA (combination therapy): Two RCTs have compared budesonide-formoterol reliever therapy versus SABA reliever therapy in mild asthma.[39,40] The SYmbicort Given as needed in Mild Asthma (SYGMA) study demonstrated that budesonide-formoterol reliever therapy reduced the rate of attacks compared with terbutaline by 64% in adolescents and adults (rate ratio 0.36, 95% CI 0.27 to 0.49).[39] In the Novel Symbicort Turbuhaler Asthma Reliever Therapy (Novel START) study, budesonide-formoterol reliever therapy reduced the rate of attacks compared with salbutamol by 50% in adults (relative rate 0.49, 95% CI 0.33 to 0.72).[40] Budesonide-formoterol reliever therapy reduced the fraction of exhaled nitric oxide (FeNO), a marker of eosinophilic airways inflammation, indicating how sensitive airways inflammation is to intermittent low doses of ICS.

Four RCTs have compared budesonide-formoterol reliever therapy with maintenance budesonide and SABA reliever therapy.[39–42] The two SYGMA studies of adolescents and adults with mild asthma showed non-inferiority between these two regimens in attack risk reduction,[39,41] whereas the two real world studies of adults, Novel START and Personalised Asthma Combination Therapy with ICS And fast onset LABA (PRACTICAL), reported a reduction in risk of severe attacks with budesonide-formoterol (relative risk 0.44, 95% CI 0.20 to 0.96, and relative rate 0.69, 95% CI 0.48 to 1.00, respectively).[40,42] The greater efficacy of the budesonide-formoterol reliever therapy regimen with the real world studies compared with the regulatory SYGMA studies may be due to participants not needing to take double-dummy placebo inhalers on a regular basis, which negate the advantage of a single inhaler used as needed to relieve symptoms.

Importantly, participants using budesonide-formoterol reliever therapy in these four RCTs used 17% to 58% of the ICS dose used by those in the budesonide group. These findings form the basis of the updated Global Initiative for Asthma (GINA) recommendations that ICS-formoterol is the preferred reliever at all treatment steps, and that SABA monotherapy is no longer recommended for adults.[43]

Whether these findings translate to childhood asthma is unknown as there have been no RCTs of as-needed budesonide-formoterol therapy in children. If comparable efficacy of this regimen is shown, then its implementation has the potential to markedly reduce asthma morbidity in children globally.

5.4 Trial hypothesis

In children aged five to 15 years with mild asthma, as-needed budesonide-formoterol (Symbicort Rapihaler) reliever therapy has greater efficacy and a favourable safety profile compared with salbutamol (Ventolin) reliever therapy.

6 OBJECTIVES AND OUTCOME MEASURES

6.1 Primary

To determine the efficacy and safety of as-needed budesonide-formoterol compared with salbutamol reliever therapy in children aged five to 15 years with mild asthma:

Outcome Measure(s)	Time point (week)
1. Asthma attacks as rate per participant per year	52

6.2 Secondary

6.2.1 To determine the efficacy of as-needed budesonide-formoterol compared with salbutamol:

Outcome Measure(s)	Time point (week)
2. Severe asthma attacks as rate per participant per year	52
3. Time to first asthma attack	Variable
4. Time to first severe asthma attack	Variable
5. Proportion of participants with at least one asthma attack	52
6. Proportion of participants with at least one severe asthma attack	52
7. Proportion of participants on each treatment step	52
8. Days in hospital	52
9. FeNO	52
10. On-treatment Forced Expiratory Volume over 1 second (FEV_1)	52
11. Asthma Control Questionnaire 5 (ACQ-5)	26 and 52
12. Days lost from school due to asthma	52
13. Days lost from work due to asthma (participant)	52
14. Days lost from work due to childcare for asthma (parent(s)/guardian(s)	52

6.2.2 To determine the safety of as-needed budesonide-formoterol compared with salbutamol:

Outcome Measure(s)	Time point (week)
15. Total systemic corticosteroid dose	52
16. Growth velocity	52
17. Adverse Events	52
18. Serious Adverse Events	52

6.2.3 To determine the cost-effectiveness of as-needed budesonide-formoterol compared with salbutamol:

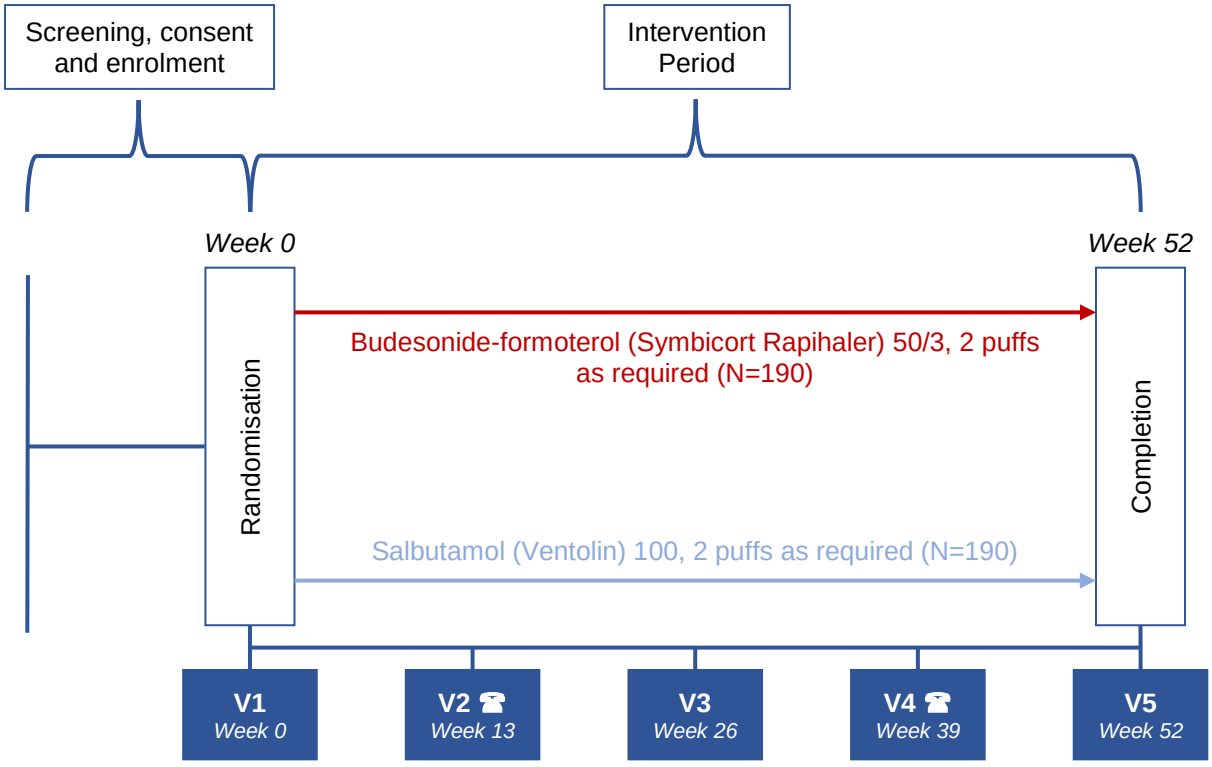
Outcome Measure(s)	Time point (week)
19. Net cost per asthma attack prevented	52

7 TRIAL DESIGN

The CARE study is a 52-week multi-centre, open-label, parallel-group, phase III, two-sided superiority RCT. Three hundred and eighty children aged five to 15 years with mild asthma on SABA only therapy will be randomised 1:1 to either:

- Intervention: budesonide-formoterol 50/3mcg metered dose inhaler (Symbicort Rapihaler) two actuations via spacer (Airflow Space Chamber Plus) as needed for relief of asthma symptoms.
- Control: salbutamol 100mcg metered dose inhaler (Ventolin) two actuations via spacer (Airflow Space Chamber Plus) as needed for relief of asthma symptoms.

Participants will be assessed for eligibility and enrolled, then allocated to the treatment regimen, if eligible, at Visit 1 (week 0). Participants will be assessed every 13 weeks and followed up for a total of 52 weeks (five visits). Visits 1, 3 and 5 will be conducted either in-person or virtually (using video conferencing software); visits 2 and 4 will be conducted via telephone.



8 PARTICIPANT INDENTIFICATION

8.1 Recruitment

Potential participants will be identified from clinical trial unit and medical databases, general practices, Emergency Departments, mailouts, and through direct/targeted advertising (including social media). Correspondence will be sent to potential participants and their parent(s)/guardian(s) inviting them to contact an Investigator if they are interested in participating.

Interested potential participants and their parent(s)/guardian(s) will be provided with an age-appropriate Participant Information Sheet (PIS). Potential participants will be encouraged to discuss the PIS and their involvement in the study with family, whānau, friends and their healthcare provider.

Once an appropriate amount of time has been given for the participant and their parent(s)/guardian(s) to consider the information (minimum 24 hours), they will be contacted by an Investigator to discuss attending a screening visit.

8.2 Inclusion criteria

8.2.1 Aged five to 15 years

8.2.2 Doctor diagnosis of asthma (parent/participant or doctor-reported) ***AND***

a. SABA use ≥3 consecutive days in the last 12 months, ***AND/OR***

b. SABA use on ≥2 days per month, on average, in the last 12 months, ***AND/OR***

c. Urgent medical review for worsening asthma in the last 12 months.

8.2.3 Registered with a General Practitioner

8.3 Exclusion criteria

8.3.1 Hospital admission (≥24 hours) for asthma in the last 12 months

8.3.2 Self-reported use of >6 SABA inhalers in the last 12 months (i.e. poor-control)

8.3.3 Any use of ICS, LABA, leukotriene receptor antagonist (LTRA), theophylline, anticholinergic agent or cromone in the last 6 months

8.3.4 Any use of systemic corticosteroids in the last 6 weeks

8.3.5 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)

8.3.6 Any known or suspected contraindications to the medications prescribed in the study or their respective excipients

8.3.7 Previous life-threatening asthma (Intensive Care Unit admission)

8.3.8 Unable or unwilling to switch from current asthma treatment regimen

8.3.9 Unable or unwilling to provide written informed consent (parent(s)/guardian(s)) or assent/consent (participant)

8.3.10 Self-reported current pregnancy or breast feeding at the time of enrolment

9 TRIAL PROCEDURES

See Appendix A for the schedules of trial procedures. There are two schedules; one that includes in-person visits (the default approach), and a second that has all visits done virtually using video conferencing software and telephone calls (these participants will not attend in-person visits at a trial site). This adaptation was made in response to the ongoing COVID-19 pandemic.

Participants who are enrolled and complete the study entirely virtually will be sent a demonstration inhaler, spacer device, and paper ACQ-5 forms prior to Visit 1. This will allow inhaler training and the ACQ-5 to be completed during the visit. It will not be possible to measure height and weight, or to perform FeNO and Spirometry assessments, for these participants.

9.1 CAREtoon sub-study

See separate CAREtoon sub-study protocol (for selected sites only).

9.2 Informed consent and assent

Informed consent and/or assent will be sought from study participants (children) and their parent(s)/guardian(s) in accordance with the following guidance:

- National Ethical Standards for Health and Disability Research and Quality Improvement
- The Care of Children Act 2004 (Section 36)
- The Code of Health and Disability Services Consumers Rights 1996 (Right 7)
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines

Both assent or consent of the participant, and consent of a parent/guardian, are required. If either the participant or their parent/guardian declines to consent/assent, the participant will not be enrolled in the study. Consent and assent are dynamic, continuous processes; Investigators will confirm the continued consent and assent of study participants and their parent(s)/guardian(s) at each study visit.[44]

9.2.1 Parent(s)/guardian(s)

Electronic consent will be obtained and confirmed by means of a parent/guardian dated e-signature, and a dated e-signature of the Investigator who presented the study information and obtained the informed consent. The parent/guardian will be provided with a copy of the e-signed Informed Consent form (either by email or paper).

Where it is not possible to gain consent electronically during an in-person visit, written consent will be obtained and confirmed by means of a parent/guardian-dated wet-ink signature, and the dated wet-ink signature of the Investigator who presented the study information and obtained the informed consent. The parent/guardian will be provided with a copy of the signed paper Informed Consent form; the original signed form will be retained at the trial site.

Only one parent or legal guardian is required to provide informed consent on the participant's behalf, though Investigators should consider the views of the other parent or legal guardians. It is reasonable for Investigators to rely on the consenting parent's/guardian's assurance that other parent(s)/guardian(s) are in agreement.[44]

If an Investigator becomes aware that the person who provided consent on behalf of the participant has lost their authority to give such consent, they should seek consent from the participant's new legal guardian as soon as possible.

9.2.2 Participants

Assent will be sought from all participants prior to enrolment. This will be confirmed by means of a participant dated e-signature (for children aged 7 years and older), and the dated e-signature of the Investigator who presented the study information and obtained the assent. A copy of the e-signed assent form will be provided to the participant's parent(s)/guardian(s).

Where it is not possible to gain assent electronically during an in-person visit, written assent will be obtained and confirmed by means of a participant-dated wet-ink signature, and the dated wet-ink signature of the Investigator who presented the study information and obtained the assent. The parent/guardian will be provided with a copy of the signed paper assent form; the original signed form will be retained at the trial site.

Participants who turn 16 years of age during the study will be asked to provide informed consent. Electronic consent will be obtained and confirmed by means of a participant dated e-signature, and a dated e-signature of the Investigator who presented the study information and obtained the informed consent. The participant and/or their parent/guardian will be provided with a copy of the e-signed Informed Consent form.

The written informed consent process will take place at the next face-to-face visit (in-person at a participating site or remotely via video conferencing software) after the participant has turned 16. If a participant is due to be contacted by telephone for their next visit (i.e. Visit 2 or Visit 4), verbal confirmation of consent to continue with be obtained and documented by the Investigator. Both consent of the participant and ongoing consent of the parent(s)/guardian(s) will be required for the participant to continue in the study.

9.3 Cultural safety

We plan to recruit Māori participants. When providing information, answering questions and taking consent, every effort will be made to ensure the concept of Manākitanga is upheld by addressing cultural sensitivity, cultural safety and Māhaki (respectful conduct), as per the 'HRC Guidelines for Researchers involving Māori' (Version 2).[45]

9.4 Screening, eligibility and enrolment

Potential participants will attend a screening visit where, if appropriate, they will undergo informed consent/assent and their eligibility will be assessed. A Screening number (sequential number at that site prefaced with the letter S and the designated site number) will be assigned during the consent/assent process. Those who do not meet the eligibility criteria will not proceed to enrolment, and if the participant is deemed ineligible, the reason will be recorded. The screening and enrolment visit may occur as a separate visit (Visit 0) or in combination with Visit 1.

9.5 Asthma Control Questionnaire, five-question version (ACQ-5)

The ACQ-5 will be administered, in accordance with the ACQ-5 user guide at visits 1, 3, and 5. An interviewer-administered version of the ACQ-5 should be used for children aged 10 years and younger.[46] Children aged 11 years and older will use the self-administered version.

9.6 Demographics, medical history and asthma review

The information collected will include the following:

Demographics (Visit 1)	• Date of birth, age, ethnicity, sex • Height and weight • Participant and/or parent(s)/guardian(s) contact details and emergency contact details • GPs contact details • National Health Index (NHI) number

Medical history (Visit 1)	• Asthma history, including:
	  ○ Age at diagnosis
	  ○ Current and previous medications for asthma
	  ○ SABA use in the last 4 weeks
	  ○ Proportion of asthma attacks in the last 12 months
	  ○ Total number of severe attacks in the last 12 months
	  ○ Prescription of systemic corticosteroids
	  ○ ED visits for asthma
	  ○ Hospitalisation for asthma
	  ○ Previous use of ICS
	  ○ Current use of an asthma action plan
	• Other medical conditions and medications
	• Smoking history and exposure:
	  ○ Participant
	  ○ Household
	If the participant is a current smoker, the Investigator will provide smoking cessation advice.
	• E-cigarette use (vaping) history

Asthma review (visits 2 to 5)	• Asthma attacks (moderate or severe) • Change in medication • Non-study asthma inhalers taken • Prescription of systemic corticosteroids • Urgent, unplanned medical reviews due to asthma • Hospitalisation (including duration of stay) • Days off school due to asthma (participant) • Days off work due to asthma (participant) • Days off work due to childcare for asthma (parent(s)/guardian(s)) • Adverse events • Serious adverse events

9.7 Weight and height

Height will be measured at visits 1 and 5 using a stadiometer and weight with electronic weighing scales. Participants will take off their shoes for both measurements. If Visit 1 or 5 take place virtually (e.g. using video conferencing software), height and weight will not be measured.

9.8 Fractional exhaled Nitric Oxide (FeNO)

FeNO will be measured in accordance with guidelines published by the ATS,[47] using a FeNObreath® device (made by Bedfont Scientific, United Kingdom), at visits 1 and 5. Appropriate infection control procedures will be followed at each study site. Participants will be advised to abstain from food, drink and strenuous exercise for one hour prior to the measurement being taken. Participants will not be required to withhold medication. FeNO will be obtained prior to spirometry being performed. If Visit 1 or 5 take place virtually (e.g. using video conferencing software), FeNO testing will not be performed.

9.9 Health economics questionnaire

See Appendix B. To be completed at visits 1, 3, and 5.

9.10 Forced Expiratory Volume over 1 second (FEV_1)

Spirometry will be performed according to standard technique using an NND Easy on-PC Spirometer,[48] at visits 1 and 5. Appropriate infection control procedures will be followed at each study site. Participants will not be required to withhold medication. Reversibility testing is not required at any visit. The results will be interpreted according to ATS criteria,[49] using GLI reference ranges. Site personnel will be trained on spirometry technique to ensure quality. Training will be completed prior to site initiation and during the study. In addition, spirometry reports will be over-read by specialists to confirm the spirometry data that can be included in the analysis dataset. If Visit 1 or 5 take place virtually (e.g. using video conferencing software), spirometry will not be performed.

9.11 Treatment allocation

9.11.1 Randomisation

At Visit 1, participants will be randomised in a ratio of 1:1 to either as-needed budesonide-formoterol or as-needed salbutamol, with stratification according to their:

- History of a severe asthma attack in the previous 12 months (0 or ≥1)
- Age group (five to 11 years; 12 to 15 years)

Randomisation will be performed using a computer-generated sequence to maintain allocation concealment. Block size will vary by site; sites anticipated to recruit larger numbers will have random blocks sizes of two and four, to a total 192 randomisations per site (48 per four level stratification variable). Sites anticipated to recruit small numbers will have a single block size of 48 per four level stratification variables, for a total of 192 randomisations per site. This will be generated by the study statistician, independent of the Investigators. When a participant is randomised they will be given a randomisation number (sequential number at that site prefaced with the letter R and the designated site number). Randomisation codes will be sequentially assigned as soon as participants are confirmed as eligible for randomisation. Randomisation codes cannot be re-used.

Where two or more participants in the same primary household are enrolled into 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 ensure compliance with the treatment regimens. When a participant is allocated to a treatment they will be given an allocation number (sequential number at that site prefaced with the letter A and the designated site number). Allocation codes will be sequentially assigned as soon as participants are confirmed as eligible. Allocation codes cannot be re-used.

Allocation concealment will be by a secure database, which contains the randomisation sequence.

9.11.2 Masking

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. Blinding is not being performed in order to maintain the potential real-world advantage of the budesonide-formoterol reliever therapy regimen (i.e. the use of a single combination inhaler only when needed). A participant's treatment allocation will only be revealed to the researchers when that participant is randomised via the electronic case report form (eCRF). The study statistician will be masked while performing the primary analysis of the primary outcome variable.

9.12 Participant information and education

9.12.1 Inhaler technique

At Visit 1, participants will be educated on correct inhaler technique with a demonstration and written instructions. Inhaler technique will be reassessed at visits 3 and 5. Participants will be re-educated as necessary (Appendix C).

9.12.2 Personalised Asthma Action Plans

All participants will be provided with a study-specific asthma action plan relating to their randomised arm (Appendix D) at Visit 1. These plans have been adapted from the Asthma and Respiratory Foundation of New Zealand asthma action plans (both child and adult versions),[50,51] with guidance from paediatric respiratory specialists and a paediatric emergency medicine physician.

The purpose of these plans is to reinforce the randomised treatment regimens, and to provide written instructions on what to do in the event of worsening asthma (including when to see a GP and when to seek emergency treatment). Asthma action plans can be reissued as appropriate at subsequent visits.

Participants will not be required to measure their peak flow or to fill in a record card every day as this may cause some participants to take their inhaler more often than is needed.

The reverse side of the asthma action plans contains a logbook for recording asthma-related events. It also contains information on how to use, and look after, the inhaler(s) and spacer device.

9.12.3 MyCap

MyCap, a mobile application extension of REDCap (Section 11.2), may be setup on participants' and/or their parent(s)/guardian(s) mobile phones. This will act as an electronic logbook, enabling participants and/or their parent(s)/guardian(s) to record events in real-time. This may be used as well as, or instead of, the paper logbook. The installation and use of MyCap is optional.

9.13 Medication dispensing and collection

See Section 10.

9.14 GP communications

A participant's GP will receive a letter from an Investigator when the participant:

- Is enrolled onto the study
- Has their treatment changed (including treatment discontinuation)
- Completes or withdraws from the study

9.15 Unscheduled visits

Participants and Investigators may arrange additional visits. Reasons for these visits include:

9.15.1 Unscheduled visit following a severe asthma attack

Acute management of a severe asthma attack is determined by the medical team treating the participant. Following discharge, participants should follow any prescribed weaning regimen (this will likely include a SABA for both treatment arms). Participants will be asked to record the dose and duration of this treatment.

Participants should contact Investigators for urgent review within seven days of an acute severe asthma attack. During this review, participants will have their standard treatment stepped up in accordance with the CARE stepwise treatment algorithms (Appendix E), if not already done so by their usual doctor or the medical team treating their acute asthma.

Investigators will only escalate treatment following a severe attack. A participant's usual doctor may choose to step up a participant's treatment for another reason, such as poor asthma symptom control. Change of treatment to non-study medication will not result in the participant being withdrawn from the study. If safe, Investigators will change the participant's inhaler medication to align with the CARE stepwise treatment algorithm (e.g. changing a beclomethasone inhaler to a fluticasone inhaler). Treatment will not be de-escalated. The GP will be informed of any change of treatment.

9.15.2 Unscheduled visit for dispensing of trial medication

If a participant or their parent(s)/caregiver(s) require additional inhalers (e.g. due to high-use, loss of inhaler(s), or inhaler(s) not working properly), they should contact their Investigator to arrange a visit as soon as practically possible.

At the visit, participants will be reviewed for AEs and SAEs and their inhaler technique assessed (with re-training as necessary). If a participant or their parent(s)/caregiver(s) report high-use, then the following action will be taken (as detailed in the asthma action plans, Appendix D):

High-use	Action
More than 6 puffs of their reliever inhaler a day, for one week	See their GP within one week to review, add, or amend their current maintenance therapy
More than 12 puffs a day	Go to the hospital or see their doctor today
More than 16 puffs a day	They need to attend ED immediately

9.15.3 Unscheduled visit for consideration of withdrawal

Participants and their parent(s)/guardian(s) have the right to withdraw from the study at any time. They do not have to provide a reason.

Investigators may withdraw a participant from the study at any time. Reasons for withdrawal include:

- Pregnancy
- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- An adverse event which results in inability to comply with trial procedures

Should an Investigator become aware that a participant wishes to withdraw, or may require withdrawal, from the study between study visits they will request attendance at an unscheduled visit. This is to take place as soon as practically possible. Participants and their parent(s)/guardian(s) will be asked to bring all dispensed inhalers to the visit.

At this visit, an Investigator will undertake an asthma review. If the participant withdraws, or is withdrawn, the visit should be conducted as for Visit 5. An exception to this is if the participant, or their parent(s)/guardian(s), declines consent or assent. In addition to Visit 5 procedures, the reason for withdrawal should be documented. If the participant and/or their parent(s)/guardian(s) declines to give a reason, as is their right, then this should be documented.

If the participant is withdrawn, they will be provided with post-trial treatment, as outlined in Section 10.9. The Investigator will inform the participant's GP of their withdrawal from the study.

9.16 Discontinuation/Withdrawal

The discontinuation/withdrawal options for participants, their parent(s)/guardian(s), and Investigators are outlined below. This information will be documented along with the reason for discontinuation and/or withdrawal on a withdrawal form. The Sponsor must be informed as soon as practical.

Participants and their parent(s)/guardian(s) who decline a final visit will be asked to return the study inhalers by post.

9.16.1 Discontinuation from the randomised treatment

- The participant will no longer take trial treatment. Their asthma care will be overseen by their usual doctor.
- The participant will continue to attend study visits and engage with study procedures.
- Data will continue to be collected from participants and their parent(s)/guardian(s). The participant's NHI number and medical records will be used to validate data for the full 52-week study period.
- If the participant discontinues trial treatment due to an adverse event or serious adverse event, the Investigator will arrange for any necessary follow-up visits or telephone calls until the AE or SAE has resolved or stabilised.

9.16.2 Discontinuation from the randomised treatment and study procedures (withdrawal)

- The participant will no longer take trial treatment. Their asthma care will be overseen by their usual doctor.
- The participant will not attend future visits or provide participant-reported data.
- The participant's NHI number and medical records will only be used to validate data collected prior to the date of withdrawal.

9.16.3 Lost to follow up

- Participants who are lost to follow up with be deemed to have discontinued from the randomised treatment and study procedures.
- The date of lost to follow up will be the date that the study team last had contact with the participant. This will be determined retrospectively at 365 days after the date of randomisation.

- The participant's NHI number and medical records will only be used to validate data collected prior to the date of lost to follow up.

9.17 End of study

The end of trial is the date of the last visit of the last participant.

The Sponsor will stop the study prematurely if any safety concerns are apparent, either arising from this study, of if the Sponsor is informed of any safety issues arising outside of this study, including but not limited to safety concerns regarding the study medications. Sites will be informed of early termination of the study due to safety concerns, as soon as possible.

In the case of safety concerns arising during the study, investigators may deviate from the protocol in order to ensure the health and wellbeing of participants. The Sponsor must be informed of any cases where the protocol is not adhered to and the reasons for non-adherence, as soon as possible. Non-adherence will be reported to the appropriate ethics committees and regulatory authorities in line with local requirements.

9.18 DCE sub-study

See separate DCE sub-study protocol (for selected sites only).

10 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

10.1 Description

Product	Drug	Actuations per inhaler	Shelf-life	Approval
Symbicort Rapihaler 50/3, AstraZeneca (AZ)	Budesonide-formoterol	120	3 months out of foil wrapping (12 months in foil)	Not currently approved in NZ
Ventolin 100, GlaxoSmithKline (GSK)	Salbutamol	200	24 months	Approved in NZ for the treatment of asthma in children
Flixotide 50, GSK	Fluticasone	120	24 months	Approved in NZ for the treatment of asthma in children
Seretide 50/25, GSK	Fluticasone-salmeterol	120	24 months	Approved in NZ for the treatment of asthma in children

10.2 IMP labelling

IMPs will be labelled according to Good Manufacturing Practices, Annex 13: Manufacture of Investigational Medicinal Products. All IMPs will be labelled with a study label, according to local regulations and requirements. The IMP will be released by the Sponsor in accordance with the IMP Supply Plan.

10.3 IMP storage

All inhalers issued during the study will be stored in accordance with Sponsor requirements, as indicated on the IMP label. The IMPs will be stored securely, with access only given to Investigators and their delegated staff and in a suitable environment. If required, the storage of IMPs may be delegated to a pharmacy. Temperature monitored storage is required for all IMPs, from receipt at site until dispensing to participant.

10.4 IMP dispensing

Participants will be issued with study inhalers at visits 1 to 4 either in person or via remote dispensing. For remote dispensing, medication will be couriered from the trial site to the participant. Receipt of inhalers must be confirmed by study staff.

The inhalers, and the number of inhalers, dispensed will vary according to treatment arm, treatment step, and age group (Appendix E). The minimum number of inhalers to be dispensed at each visit is listed below.

10.4.1 Budesonide-formoterol treatment arm

Treatment step	Inhaler	Number issued per visit
1	Symbicort Rapihaler 50/3	2
2	Symbicort Rapihaler 50/3	4
3	Symbicort Rapihaler 50/3	6

10.4.2 Salbutamol treatment arm

Treatment step	Inhaler	Number issued per visit
1	Ventolin 100	2
2	Flixotide 50 (5 to 11 years)	2
	Flixotide 50 (12 to 15 years)	4
	Ventolin 100	2
3	Seretide 50/25 (5 to 11 years)	2
	Seretide 50/25 (12 to 15 years)	4
	Ventolin 100	2

Delivery of medication in both arms will be via pressurised metered-dose inhalers (pMDIs) with spacer (Airflow Space Chamber Plus). Spacers will be issued at Visit 1 and subsequent visits, if required.

Participants will be advised not to share their allocated inhalers and not to use other non-study inhalers or nebulisers, unless indicated by their doctor. If a participant does use a non-study inhaler, or nebulisers, they will be asked to document this. Participants who use non-study inhalers or nebulisers will not be withdrawn from the trial.

10.5 IMP collection

Inhaler medication will be returned at all subsequent visits after Visit 1. For inhalers with dose counters, the number of actuations remaining should be recorded. Returned medication will be stored at site until the Sponsor confirms it may be destroyed.

10.6 Adherence to randomised treatment regimen

Adherence to the randomised treatment regimens will be captured at study visits through participant self-reported inhaler use. Non-adherence will not result in withdrawal.

10.7 Accountability of the trial treatment

IMP should be used only in accordance with the protocol. Site personnel will be required to record all receipt, dispensing and collection activity regarding IMPs in addition to ensuring delivery documentation is retained at site. Used or unused IMP may be destroyed by site personnel only after approval has been provided by the Sponsor. Destruction should be documented and performed at site, or if not possible, at a site approved by the Sponsor, according to local regulations.

10.8 Concomitant medication

Concomitant medications will be reviewed at the screening visit to ensure the participant fulfils the eligibility criteria in respect to current use of asthma medications. Concomitant medications will then be reviewed and updated during each study visit. Should a participant be prescribed additional asthma treatments, this will be documented, and the participant will remain in the study.

10.9 Post-trial treatment

At Visit 5 (52 weeks or withdrawal), all participants will be given one reliever inhaler and a prescription for one additional reliever inhaler. Participants who have been escalated to maintenance therapy during the trial will also receive a prescription for a maintenance inhaler.

Post-trial treatment will differ according to age group (<12 years or ≥12 years) and treatment step. The proposed post-trial treatment is outlined below. This may be amended to comply with NZ asthma guidelines at the time of participant study completion or withdrawal. Participants will be advised to see their GP within one month of completing the study to review their ongoing asthma therapy.

All participants will receive a relevant NZ Asthma and Respiratory Foundation asthma action plan. This will detail the prescribed regimen.

10.9.1 Budesonide-formoterol treatment arm

Treatment at the end of the trial	Post-trial treatment (5 to 11 years)	Post-trial treatment (12 to 15 years)
Budesonide-formoterol (Symbicort Rapihaler 50/3) as needed	Salbutamol (Ventolin), 2 actuations as needed	Budesonide-formoterol (Symbicort Turbuhaler 200/6), 1 actuation as needed
Very-low dose budesonide-formoterol (Symbicort Rapihaler 50/3) maintenance and as needed	Maintenance fluticasone (Flixotide 50) 1 actuation twice daily, plus salbutamol (Ventolin 100) 2 actuations as needed	Budesonide-formoterol (Symbicort Turbuhaler 200/6), 1 actuation as needed
Low-dose budesonide-formoterol (Symbicort Rapihaler 50/3) maintenance and as needed	Maintenance fluticasone-salmeterol (Seretide 50/25) 1 actuation twice daily, plus salbutamol (Ventolin 100) 2 actuations as needed	Low-dose budesonide-formoterol (Symbicort Turbuhaler 200/6), 1 actuation twice daily and as needed

10.9.2 Salbutamol treatment arm

Treatment at the end of the trial	Post-trial treatment (5 to 11 years)	Post-trial treatment (12 to 15 years)
Salbutamol (Ventolin 100) as needed	Salbutamol (Ventolin), 2 actuations as needed	Budesonide-formoterol (Symbicort Turbuhaler 200/6), 1 actuation as needed
Maintenance fluticasone (Flixotide 50) plus salbutamol (Ventolin 100) as needed	Maintenance fluticasone (Flixotide 50) 1 actuation twice daily, plus salbutamol (Ventolin 100) 2 actuations as needed	Budesonide-formoterol (Symbicort Turbuhaler 200/6), 1 actuation as needed
Maintenance fluticasone-salmeterol(Seretide 50/25) plus salbutamol (Ventolin 100) as needed	Maintenance fluticasone-salmeterol (Seretide 50/25) 1 actuation twice daily, plus salbutamol (Ventolin 100) 2 actuations as needed	Low-dose budesonide-formoterol (Symbicort Turbuhaler 200/6), 1 actuation twice daily and as needed

11 DATA COLLECTION AND MANAGEMENT

11.1 Data collection

An electronic Clinical Data Management Application (CDMA) created using REDCap will be used to enable study data collection. Site staff will be given appropriate access to enter data into the CDMA after they have received appropriate training.

The electronic CDMA will be designed to collect data in real time during clinic visits. Data will also be collected via MyCap, and/or through documentation on the back of the participant's asthma management plan or, if unrecorded by the participant, through self-report at each study visit. Where data are collected on paper, or derived from other sources, site staff will complete study data entry into the CDMA on an ongoing and timely basis.

For the primary outcome measure, data collection will be through participant-reported data/logs, and through review of GP electronic medical records, and the hospital, ambulance and After-Hours electronic records in each region. We will also access prescription data using the participants NHI number. Participant-reported data will include a log of asthma attacks (urgent medical review and prednisone/prednisolone use), days lost from school/work due to asthma, and use of additional prescribed asthma medications. Medical records and self-reported data will be reviewed together.

Discrepancies and queries raised by monitors or via pre-programmed checks will be arbitrated by investigators using predefined criteria.

11.2 Source Data

Source data refers to where data are first recorded, and from which participants' study data are obtained. Source documents include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, radiographs, correspondence and audio recordings. Study data will be

collected into a CDMA, in which entries will be considered source data if the CDMA is the site of the original recording (e.g. there is no other written or electronic record of data).

It is the intention of the Sponsor to capture as much study related data as possible (including informed consent) using e-source, through direct data capture into a REDCap-based CDMA. REDCap is a secure, HIPAA (United States Health Insurance Portability and Accountability Act 1996) compliant web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages, including de-identified data sets; and 4) procedures for importing data from external sources.[52,53] Where it is not possible for source data to be captured via direct data capture, investigators will transcribe the data from the source into the CDMA.

11.3 Electronic Case Report Form (eCRF) Data

An eCRF (an application held in REDCap) will hold data that is required for analysis. Specified data held in the CDMA will be pulled through to the eCRF. During the process of the data pull, the data from the CDMA will be rendered non-identifiable, with each participant identified by a unique study ID within the eCRF.

11.4 Access to Data

Direct access to source and study data will be granted to authorised representatives from the Sponsor, and the regulatory/ethics authorities to permit trial-related monitoring, audits and inspections. Investigators will have continuous access to the source data they have entered into the CDMA. The investigator and site retain ownership of the data they have entered. The Sponsor will have access only to data held within the eCRF, with the exception of the delegated study monitor(s), who will have access to source data held in the CDMA, for the purpose of enabling trial-related monitoring. Sponsor REDCap Administrators may technically access the CDMA data, as their access is unrestricted. Administrators will not access the CDMA except where specifically required to do so. The system audit trail will record Administrator access to CDMA data and this will be checked as part of Sponsor monitoring activity to ensure compliance.

11.5 Record keeping

Data contained within the CDMA and eCRF will be held on Sponsor controlled secure servers, hosted by Amazon Web Services, located in Sydney, Australia. Summarised trial related data (not containing any particpant identifiable data) may also be held on Sponsor controlled secure servers in NZ, and Sydney or Melbourne, Australia.

The following records will be stored/ archived for 10 years after the youngest child in the study turns 16 years old or 15 years after the completion of the trial, whichever is longer:[44]

- Source and essential documents
- Study data held within the eCRF
- Essential documents held in the Trial Master File (TMF)

Investigators may continue to access data held within the CDMA after database lock/ data archive has occured. The data will be read-only to prevent unauthorised changes. Access requests will be facilitated by the Sponsor, including access in the case of a regulatory audit.

11.6 Participant Confidentiality

Data will be collected, used and stored in accordance with applicable Site and Sponsor standard operating procedures (SOPs) and the Health Information Privacy Code 1994, the Code of Health and Disability Services Consumers Rights 1996, and the Bill of Rights Act 1990.

The study staff will ensure that the participant's privacy is maintained. Participant identifiable data will be captured as part of source data, which will only be accessible to authorised Site staff members.

Participant identifiable information including name, contact details, NHI number, date of birth and ethnicity will be collected in the CDMA, which is designed to collect all the study information at a site. The CDMA is accessible only to site staff; sponsor staff cannot access the CDMA unless with specific permission, thereby maintaining participant confidentiality.

Protocol-defined data will be extracted from the CDMA into the eCRF, which can be accessed by sponsor staff. Limited personal information (e.g. date of birth and demographic details) will be pulled into the eCRF as they will be required as part of the study analysis. Name and contact details will not be pulled into the eCRF; participants will be identified by a unique participant number. The CDMA and eCRF are encrypted, secure systems, protected by unique username and password requirements for log-in, which are only provided to trained study staff.

Individual patient GP address is being captured so that participants' GPs can be informed of their involvement in the trial.

The NHI number will be collected to assess the agreement between participant reported details and electronic health records of attacks of asthma. This will be outlined specifically to the participants and their parent(s)/guardian(s) in the PIS-CF so that they are aware of this provision of their data and can provide their consent to its use in this way. The Sponsor will only use a participant's NHI number and other personal information for the purposes outlined above. No study reports will contain any information that could individually identify a study participant.

Data recorded in the CDMA and CRF (including MyCap) will be securely stored on servers in New Zealand and Sydney, Australia.

Questionnaire data will be pulled into the eCRF, identified by unique study identifier, but no names or signatures will be stored in the eCRF.

The Sponsor (via the Study Monitor) will have access to the identifiable source data at site, for monitoring purposes, to ensure the study is being run in compliance with GCP and the protocol.

12 SAFETY REPORTING

12.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening (an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • In the case of a product with a marketing authorisation, in the Medsafe Datasheet for that product • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

To avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which *may* be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".

A deterioration in asthma symptoms (wheeze, cough, chest tightness, dyspnoea, breathlessness and phlegm) will be recorded as AEs if:

- SAE criteria are met
- The participant is removed from treatment due to the deterioration in asthma symptoms
- The symptoms are new to the participant or not consistent with the participants pre-existing asthma history, as judged by the Investigator

12.2 Causality

The relationship of each adverse event to the study medication must be determined by a medically qualified individual according to the following definitions:

Related	The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause
Not related	The adverse event is produced by the participant's clinical state or by other modes of therapy administered to the participant

12.3 Severity

The severity of events will be assessed on the following scale:

Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL (e.g. unable to participate in usual sport or attend school)
Grade 3	Severe	Medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalization indicated; disabling; limiting self-care ADL (i.e. bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life-threatening	Consequences indicating urgent intervention
Grade 5	Death	Related to AE

12.4 Procedures for recording adverse events

All AEs occurring during the trial that are observed by the investigator or reported by the participant, will be recorded on the eCRF, whether attributed to trial medication or not.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary. AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

The Sponsor is responsible for reporting AEs in the intervention arm (budesonide-formoterol) to Medsafe.

12.5 Reporting procedures for serious adverse events

All SAEs, whether or not they are considered causally related to the IMP, must be reported to the Sponsor within 24 hours of the Study Team becoming aware of the event. All SAE information must be recorded on the SAE form within the eCRF, or scanned and emailed to the Sponsor.

The Sponsor will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Medical Monitor on a weekly basis. Additional and further requested information (follow-up or corrections to the original case) may be captured within the SAE form or scanned and

emailed to the Sponsor. Follow-up/new information is required within the same reporting timeline, i.e. within 24 hours of the Study Team becoming aware of the new information.

SAEs will also be reviewed by the Data and Safety Monitoring Committee (DSMC) in accordance with their Charter.

The Sponsor is responsible for informing the HDEC, Medsafe and/or the Regulatory Authority of the SAE, as per local requirements.

SAEs related to the IMP(s) will be provided to AstraZeneca within 24 hours of Sponsor knowledge, on an ongoing basis, as individual case reports. SAEs unrelated to the IMP will be provided to AstraZeneca as individual case reports on an ongoing basis. SAEs that do not require expedited reporting to the regulatory authorities will still be reported to AstraZeneca as individual case reports, on an ongoing basis.

At the end of the Study, a final summary line listing of all SAEs notified to the regulatory authorities and/or AstraZeneca during the Study, will be provided to AstraZeneca to enable reconciliation of safety information held by AstraZeneca for its product.

12.6 Expectedness

Expectedness will be determined according to the current version of the Medsafe Datasheet or Investigator Brochure, for each applicable medicinal product respectively.

12.7 Reporting procedures for SUSARs

All SUSARs will be reported by the Sponsor to CARM (Centre for Adverse Reactions Monitoring), Medsafe and the HDEC as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

SUSARs will be reported to AstraZeneca at the same time these events are notified to the Regulatory Authorities.

12.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Sponsor.

If a participant becomes pregnant during the course of the study, they will be withdrawn from the study and their ongoing care will be managed by their usual doctor.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the study product may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. The outcome of all pregnancies (spontaneous miscarriage, termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented wherever possible.

If any pregnancy occurs during the course of the study, then the Investigator should inform the Sponsor no later than 24 hours of when he or she becomes aware of it.

The Sponsor will work with the Investigator to ensure that all relevant information is captured within the eCRF. If a pregnancy results in SAE criteria being met, information should be reported in accordance with SAE timelines stated above. All other pregnancy outcomes should be reported within 30 days of birth.

As the study medication products are not contraindicated in pregnancy, the pregnancy status of participants' partners will not be recorded.

12.9 Data and Safety Monitoring Committee

An independent DSMC will be formed to safeguard the interests of trial participants, assess the safety and efficacy of trial interventions, and monitor the overall conduct of the trial. The conduct and responsibilities of the DSMC are outlined in the DSMC charter.

The DSMC will review trial conduct data (e.g. recruitment, withdrawals, protocol deviations, and serious breaches) and safety data (e.g. SAEs, SARs, and SUSARs). The DSMC will also review the results of the interim safety assessment and/or analysis (Section 13.5.1). The DSMC may recommend termination of the trial, however the TSC will make the final decision.

13 STATISTICAL ANALYSIS

A Statistical Analysis Plan (SAP) will be developed by the Sponsor and approved by the study statistician. This SAP will be finalised prior to database lock. All participants who are enrolled will be included in the analysis. Any deviation(s) from the original statistical plan will be described and justified in the final report. The following information is a summary of the SAP.

13.1 Primary outcome variable analysis

This will be by intention-to-treat superiority analysis by a biostatistician masked as to treatment allocation. The primary analysis is by estimation of the relative rate of total asthma attacks per participant per year 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 score, trial site, time from receipt of IMP, 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. Ethnicity will be treated as: European, Māori, Pacific, Other; if there are low numbers, particularly for other, we will merge with European. For illustrative purposes age will also be considered as a dichotomous variable split by age group (five to 11 years; and 12 to 15 years).

13.2 Secondary outcome variable analyses

The following methods will be used:

13.2.1 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

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.

13.2.2 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

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.

13.2.3 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

13.2.4 ANCOVA with baseline (where taken) as a continuous covariate

- FEV_1
- FEV_1 z-score
- FEV_1 % predicted
- FEV_1 prediction value (GLI values)
- FeNO (on the logarithm-transformed scale)
- Growth velocity

13.2.5 ANCOVA and mixed linear models for repeated measures by time:

- ACQ-5

13.2.6 Analysis dependent on data distribution:

- Total oral corticosteroid dose

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.

13.2.7 Descriptive data

- Total ICS dose (for inhalers with dose counters)

13.2.8 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.

13.3 Sub-group and sensitivity analyses

13.3.1 Sub-group analyses will be performed for three outcome variables: rate of asthma attacks, rate of severe attacks, and ACQ-5. In these sub-group analyses the differential effect of treatment on outcome will be explored with each of the following potential moderating variables:

- SABA use at baseline, measured as the average number of occasions per week of self-reported SABA use in the four weeks before enrolment
- Severe asthma attack in the previous 12 months
- Age at baseline
- Age group (five to 11 years; 12 to 15 years)
- Sex
- Ethnicity
- Trial site
- Household smoking status
- Baseline ACQ-5 score (for asthma attacks and severe asthma attacks outcomes only)
- Baseline FeNO
- Baseline FEV_1 % predicted

13.3.2 For illustration on the Forest Plot, baseline ACQ-5 score, baseline FeNO, and baseline FEV_1 % predicted will be dichotomised at the median value of the control arm.A sensitivity analysis will be performed to check for effect modification between participants enrolled virtually versus in-person.

13.4 Sample size calculation

The primary outcome is the relative rate of asthma attacks between the treatment groups. The annualised attack rate for children, similar to those to be recruited for this study, who use SABA monotherapy, is not available. The TREXA study reported an annualised attack rate of 0.84. However, the participants in this study were more unstable than our participants due to withdrawal of ICS treatment, and so this rate is unreasonably high.[30] A more reasonable estimate has been determined through extrapolation of relevant studies:

- The ASIST study showed an annualised attack rate of 0.28 in children on maintenance ICS plus SABA reliever.[31]
- In Novel START we showed that the annualised attack rate in the ICS-LABA group 1) did not differ significantly from the rate in the maintenance budesonide group (Relative Rate (RR) 1.12, 95% CI 0.70 to 1.79, P=0.65), and 2) was lower than that in the SABA only group (RR 0.49, 95% CI 0.33 to 0.72, P<0.001).[40]
- Budesonide-formoterol maintenance and reliever therapy (SMART) reduced the risk of severe attacks compared with regular budesonide-formoterol plus terbutaline reliever therapy to a greater extent in children aged four to 11 years than that observed in adults and adolescents (risk ratio 0.28, 95% CI 0.14–0.53 vs. 0.59, 95% CI 0.49–0.71, respectively), suggesting potentially greater efficacy of the “anti-inflammatory reliever” component in children.[36,37]

The table below shows the total number of participants in a two-arm study, with equal proportions in each arm, to detect nominated relative rates. The relative rate of attacks for budesonide-formoterol reliever therapy versus salbutamol reliever therapy in adults is between 0.40 and 0.49.[39,40] We have chosen the sample size to detect a more conservative relative rate than this of 0.55. By simulation from

appropriate Poisson distributions we estimate this need 160 participants in each group, a total recruitment of 320 participants to achieve 90% power, two-sided alpha of 5%, to detect a difference in rates between 0.28 in the active-treatment arm and 0.51 in the SABA-only arm. Accounting for a dropout rate of 20% gives a total sample size of 380 participants (190 in each arm).

Rates		Total Sample Size	
Relative Rate (cf. 0.28)	Control arm rate	80% Power	90% Power
0.4	0.7	90	120
0.45	0.62	120	160
0.5	0.56	170	220
0.55	0.51	240	320

The study is also powered for the key secondary outcome of severe asthma attacks. NZ data from 2018 show that 27,796 six to 12-year olds on salbutamol monotherapy had a severe attack (prescription of oral steroids). This represents an annual rate of 0.32. By simulation from appropriate Poisson distributions, 160 participants in each group, a total recruitment of 320 participants, has 91% power, two-sided alpha of 5%, to detect a difference in rates between 0.32 in the salbutamol arm and 0.144 in the budesonide-formoterol arm. This represents a rate reduction of 0.45, which is a conservative estimate based on the rate ratio of 0.36 and risk reduction of 0.40 with budesonide-formoterol vs. SABA reliever therapy in the two adult studies.[39,40]

13.5 Interim statistical analyses

Two masked interim assessments and/or analyses are planned after 60% (N=228) of trial participants have been recruited.

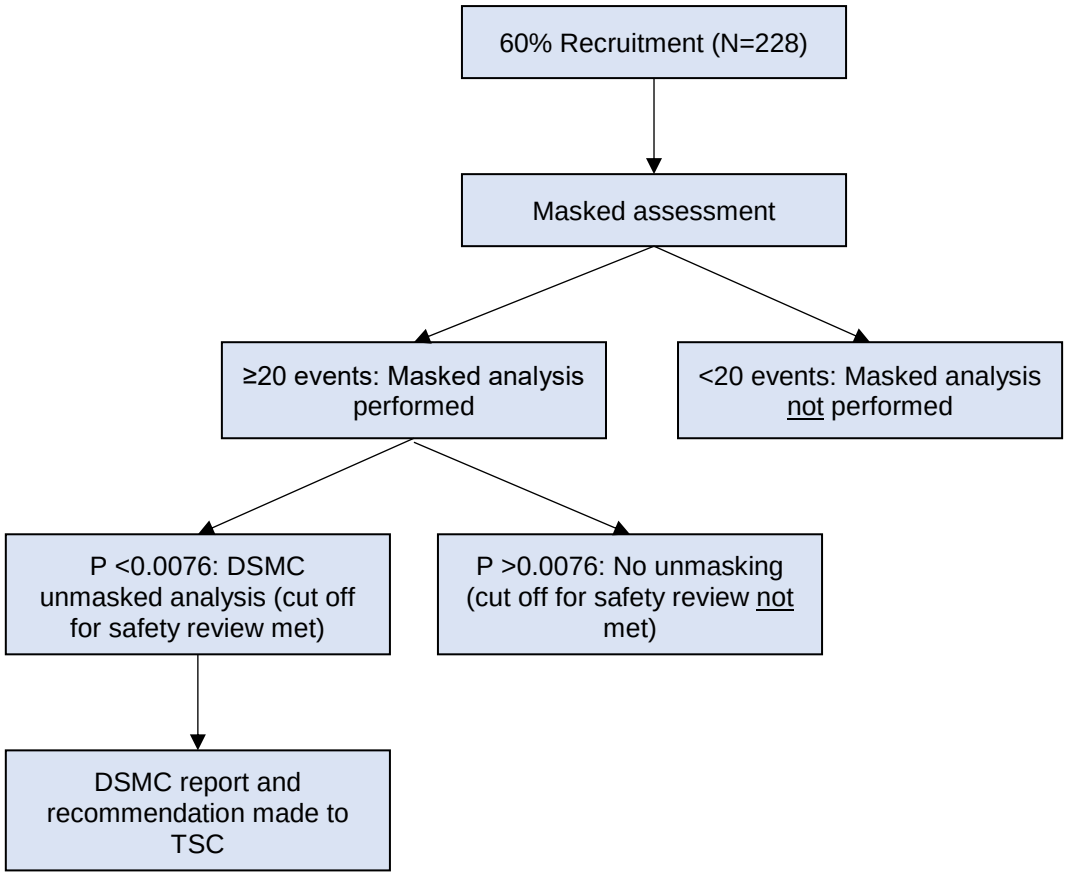
13.5.1 Safety assessment and/or analysis

An interim safety statistical assessment and/or analysis will be conducted by the study statistician, masked to treatment allocation, for all unplanned hospital admissions (of ≥24 hours duration) for asthma. The data for assessment and/or analysis will be provided without the patient ID code, but with the masked randomised treatment code, e.g. treatment 1 or treatment 2.

The calculated interim P-value for performing a safety review of the study was estimated using the 1d98 program, and is 0.0076, based on an analysis after 60% of recruitment and a final assessment, and using a two-sided O'Brien-Fleming boundary. The trigger for an assessment of the difference between randomised groups will be if there are a total of 20 hospital admissions for the two randomised groups combined (N=228). In this scenario there are 5 possible combinations of different proportions in the two randomised arms where the P-value for the comparison is less than 0.0076. The least extreme scenario is if 4/114 (3.5%) in one arm and 16/114 (14%) in the other arm have a hospital admission, P=0.004.

Of note, the rate of asthma-related hospital admissions in NZ for children aged five to 14 was 2.2% (2016/17).[54] This figure includes children with more severe asthma. In addition, the rate of asthma-related hospitalisations in two adult studies of ICS-formoterol versus SABA was 0.8.[39,50] The rate ratio for asthma-related hospitalisations in children (<15 years) versus adults (30 to 64 years) is 2.7;[2] 0.8 x 2.7 = 2.2%. In all of the 5 extreme scenarios in a triggered analysis based on 20 or more events after 228 participants are recruited this is the approximate rate in one of the arms for these scenarios, namely 3.5% or less.

The DSMC will review the results of the interim safety assessment and/or analysis. If the findings of the safety analysis indicate a safety review is necessary, then termination of the trial will be considered. The TSC will make the final decision on whether or not to terminate the trial.



13.5.2 Sample size re-estimation

A masked assessment of the rate of asthma attacks in the two randomised arms will be performed. We will estimate a 95% CI 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, if resources permit.

Sample size re-estimation was conducted as outlined above, after the 228th participant had been randomised. Based on the point estimate and 95% confidence interval of the highest exacerbation rate, and with 90% power to detect a relative rate of 0.55, a sample size of 340 (170 per arm) is required. Factoring in a withdrawal rate of 4.8% (the rate at the time of the interim re-estimation), this gives a sample size estimate of 360 (180 per arm), allowing for drop-outs.

The Trial Steering Committee therefore agreed that the sample size would be reduced from 380 to 360.

13.6 Statistical significance

The level of statistical significance is p≤0.05.

13.7 Procedure for accounting for missing, unused, and spurious data

Data will continue to be collected from participants if their treatment regimen is changed, or if they withdraw from the study, unless they rescind their consent/ascent, in order to minimise missing data. GP and self-reported data will be reviewed together; discrepancies will be arbitrated by investigators using predefined criteria. For repeated measured analyses of continuous variables, mixed linear models will be used which assume missing data are missing at random. Otherwise imputation will not be used.

For the primary outcome participants with no time of observation will be given zero weight in the analysis, i.e. this will be a complete case analysis.

13.8 Economic analysis

The annual cost of asthma (all ages) to the NZ economy is estimated to be $1,017,924,605. This is a minimum cost and does not include the direct cost of ED visits for asthma, work days lost, or the long term costs associated with time off school.[2]

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. To undertake this extension, consideration will be given to the addition of specific questions (e.g. the negative affect consequences of an attack) to our pre- and post-treatment questionnaires for families. This extension may prove valuable beyond the current study by demonstrating how factors such as distress can be incorporated into an evaluation of treatment options.

13.9 Ethnicity analysis

Asthma disproportionately affects Māori children compared with NZ European children (rate ratio 1.36).[2] Health services are less accessible for Māori and there is inequity in the quality of services provided; Māori children are less likely to receive preventers (ICS), rendering them overly reliant on their SABAs.[55] This may contribute to the much higher hospitalisation rates for asthma in Māori children. Inclusion of ICS with a beta-agonist as default (i.e. ICS-formoterol) has the potential to mitigate this risk. Evidence from adult studies shows that this approach reduces asthma attacks, and is at least as effective as maintenance ICS plus SABA at preventing severe asthma attacks in Māori adults.[42,50] Additional analyses will be undertaken to explore differences in outcomes according to ethnicity, in particular looking at outcomes of participants identifying as Māori or Pacific. This analysis will be defined in an additional analysis plan.

13.10 Combined analysis

We plan to undertake a combined analysis of data from this study and other similar RCTs.

13.10.1 If individual patient data are available:

Data will be combined for comparison of the as-needed budesonide-formoterol and the SABA reliever regimens. The rate of asthma attacks per participant per year will be the primary outcome variable, and the rate of severe asthma attacks per participant per year a key secondary outcome variable.

The primary combined analysis will be an ‘intention to treat’ superiority analysis of the primary outcome variable by Poisson regression with an offset for the time of observation. 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, including: age, age group (11 years and under; 12 to <18 years), sex, ethnicity, baseline ACQ-5 score, severe attack in the previous year, and baseline FeNO. This will account for different distributions of these variables in the treatment groups and to increase precision of the estimates of differences. If the outcome data are sparse it may not be possible to include all of the confounding variables for the sensitivity analysis.

13.10.2 If only summary data are available:

Inverse variance weighted meta-analysis will be used, with the rate of asthma attacks per participant per year the primary outcome variable, and the rate of severe asthma attacks per participant per year as a key secondary outcome variable.

The meta-analyses of the rate ratios for the number of asthma attacks and the number of severe asthma attacks will use the logarithm-transformed estimates of rate and their confidence intervals to estimate the variance, on the logarithm scale, for the estimates. The variances will be estimated by dividing the difference between the upper and lower confidence bounds by 3.92, and squaring the results. Back-transformation by exponentiation gives estimates back on the scale of rate ratios.

14 QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to GCP, as defined within the study Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures/the Monitoring Plan, the Monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Data will be monitored by the DSMC, as outline in this document and the DSMC Charter.

The Trial Management Group (TMG) will meet regularly to discuss the progress of the trial and for the purpose of assuring quality, in their role of executing the function of Sponsor. The TMG will be formed of Sponsor staff with relevant expertise in conducting multi-centre trials.

The TSC will meet formally every six months to discuss the progress of the trial, including DSMC correspondence and the outcome of site monitoring visits if appropriate.

Site initiation visits will be performed by Sponsor representatives, including the Clinical Trial Monitor to ensure that the site is ready to begin recruiting for the study; all necessary approvals (ethics/ regulatory/ research office etc.) are in place prior to the first patient enrolment; training has been completed on data collection, as well as study specific procedures, such as spirometry, FeNO and the checking and training of inhaler technique.

The appropriate manuals and guidelines will be issued to sites in order that they are able to perform the study as per protocol. Any additional training for study procedures will be performed as necessary. The Principal Investigator will maintain a record of all individuals involved in the study.

15 PROTOCOL VIOLATIONS

The Health and Disability Ethics Committee (HDEC) SOPs (December 2019) define a protocol violation as a “deviation that may affect participants’ rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Deviations/violations may occur without the knowledge or permission of the sponsor or the CI, and may constitute fraud or misconduct.”

Violations are events that are likely to affect to a significant degree any of the following:

- The safety or physical or mental integrity of participants
- The scientific value of the study
- The conduct or management of the study
- The quality or safety of any medicine or item used in the study

In the event that a protocol violation is suspected the Sponsor must be contacted within 1 working day. In collaboration with the Investigator the violation will be reviewed by the Sponsor and, if deemed appropriate, it will be reported to the responsible HDEC, regulatory authority, and local governance body (as applicable) within seven working days.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

16.2 Guidelines for Good Clinical Practice

The Investigator will ensure this trial is conducted in accordance with relevant regulations and with GCP.

16.3 Research involving children and young people

This trial has been designed in accordance with ethical guidelines for health research with children and young people, specifically: the NZ National Ethics Advisory Committee's *Ethical Guidelines for Intervention Studies: Revised Edition* (2012),[56] and the NZ Ministry of Health's *Operational Standard for Ethics Committees: Updated Edition* (2006).[57]

16.4 Approvals

This study requires submission to Medsafe (via the Standing Committee on Therapeutic Trials) under Section 30 of the Medicines Act 1981, as Symbicort Rapihaler is not an approved product in New Zealand.

Ethical Submission will be made to one of the Health and Disability Ethics Committees of New Zealand. The opinion/ approval of the Ethics Committee will be given in writing. Locality approval must be granted before any participants are recruited, as per Ethics Committee guidelines. The Ethics Committee should approve all advertising used to recruit patients for the study. Approval for the study will also be sought from an appropriate Māori Consultation body, and such approval will be given prior to Locality approval being issued.

The Chief Investigator will submit all substantial amendments to the original approved documents to the HDEC for review and approval. The Sponsor should approve any modifications to any documents provided to the HDEC.

16.5 Reporting

The Chief Investigator shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the HDEC and Sponsor. In addition, a Notification of Completion form and final report will be submitted to the HDEC and Sponsor, in accordance with their requirements.

The Chief Investigator shall also submit six-monthly study progress reports to Medsafe, as well as details of any amendments to the trial, and a final report at the end of the study.

16.6 Expenses and inducements

The parents(s)/guardian(s) of participants will be reimbursed for expenses resulting from participation in this trial. The reimbursement will cover the cost of expenses such as fuel and parking, or internet/data use for attending in-person visits (scheduled and unscheduled). The reimbursement amount will be approved by the ethics committee and the Sponsor to ensure it is appropriate.

Participants (i.e. children) will receive an ID badge and stickers (Appendix F) at Visit 1 (0 weeks), denoting their status as an Honorary Researcher, a $30 gift card or book voucher (koha) at Visit 3 (26 weeks), and a certificate (Appendix G) at Visit 5 (52 weeks or withdrawal) as a thank you for participating in the study.

Participants and their parent(s)/guardian(s) will not receive any financial payments for participating in this study, in line with HDEC guidance.[56] This information will be included in the PIS-CF.

16.7 Ethical Considerations

Other ethical considerations include:

- Clinicians and researchers with extensive experience of working with children have been involved in the design of this trial, and will continue to supervise and oversee its conduct (e.g. through the TMG, TSC, and DSMC).
- All patients randomised to the control arm will receive as-needed salbutamol, the current standard treatment for children with mild asthma on ‘Step 1’ therapy.
- Participants deemed to be at ‘high risk’ will be excluded.
- Participants enrolled in the study will receive regular follow up (a total of five scheduled study visits), asthma education (including inhaler technique), and lung function testing. They will also be able to contact an Investigator directly regarding any study-related queries.
- All participants will receive study- and treatment-specific asthma action plans, which detail what to do in the event of worsening asthma.
- The use of a pMDI with spacer is the preferred mode of delivery of beta-agonists during acute attacks of asthma in children.[51]
- Investigators may choose to withdraw a study participant at any time due to safety concerns.
- The prescribed randomised treatment can be modified at any stage during the study if it is considered the child needs an increase in their routine treatment. This decision will be taken by the Investigators or GP on a per participant basis and has been protocolised to ensure consistency (Appendix D).

17 FINANCE AND FUNDING

17.1 Funding

This study is funded by the Health Research Council of New Zealand (20/389) and Cure Kids.

17.2 Investigational Medicinal Product

AZ will provide Symbicort Rapihaler 50/3 inhalers and dummy Symbicort Rapihaler inhalers (for education of inhaler technique) only.

17.3 Insurance

This study is not being conducted for the benefit of a drug manufacturer or distributor and therefore clinical trial insurance to cover participant injury due to participation in the study is not required. Participants may claim under the Accident Compensation Act 2001 for injury sustained during the study, if appropriate.

18 PUBLICATION POLICY

The study findings will be published by the Sponsor, in a scientific peer reviewed journal, according to the International Committee of Medical Journal Editors recommendations. The Investigators listed on page one will be listed as authors, in recognition of their contribution to the design, implementation and oversight of the study.

Results of the study will be sent to participants on request (once available) and will be made available on a publicly available trial registry website, recognised by the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) as a Primary Registry.

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20 APPENDIX A: SCHEDULE OF TRIAL PROCEDURES

Schedule of trial procedures: Visits 1, 3 and 5 in-person (default)

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
CAREtoon sub-study[*]	X[^]	X					
Confirm informed consent/ assent	X[^]	X[≠]	X	X	X	X	
Inclusion/exclusion criteria check	X[^]	X[≠]					
Enrolment	X[^]	X					
ACQ-5		X		X		X	
Medical history and demographics		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	
FeNO[#]		X				X	
Health economics questionnaires		X		X		X	
FEV_1		X				X	
Randomisation		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 koha				X			
Provide badge (V1) and certificate (V5)		X				X	
DCE sub-study[*]						X	

*Selected sites only. ^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. #FeNO must be performed prior to spirometry. A/R, as required; N/A, not applicable.

Schedule of trial procedures: Visits 1, 3, and 5 done virtually

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
Send demonstration inhaler, spacer device, and ACQ-5 forms to participant prior to visit	X						
Confirm informed consent/ assent	X^	X≠	X	X	X	X	
Inclusion/exclusion criteria check	X^	X≠					
Enrolment	X^	X					
ACQ-5		X		X		X	
Medical history and demographics		X					
Asthma review (including review of MyCap and paper logbook): *(vii)* Asthma attacks *(viii)* AEs *(ix)* SAEs *(x)* Medication changes (including use of additional medication) *(xi)* Days lost from school due to asthma *(xii)* Days lost from work due to asthma (participant) or for childcare due to asthma (parent(s)/guardian(s))			X	X	X	X	A/R
Health economics questionnaires		X		X		X	
Randomisation		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	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 koha				X			
Provide badge (V1) and certificate (V5)		X				X	
DCE sub-study*						X	

^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. A/R, as required; N/A, not applicable.

21 APPENDIX B: HEALTH ECONOMICS QUESTIONNAIRE

The following health economics questionnaires will be administered to participants and their parent(s)/guardian(s) in the presence of an Investigator, who may provide clarification if required.

Instructions for all questions / visits:

- *This questionnaire should be completed by the participant's parent or guardian*
- *Please answer the following questions in relation to the child in the current study.*
- *You can ask the study team for help if you are unsure of anything**.***

For all questions:

A severe asthma attack is defined as:

- *Worsening asthma leading to an urgent, unplanned medical review (e.g. primary care or ED visit) or hospital admission; resulting in the prescription of systemic corticosteroids (tablets, suspension or injections – e.g. oral prednisone).*

A non-severe asthma attack is defined as:

- *Worsening asthma leading to an urgent, unplanned medical review (e.g. primary care or Emergency Department visit) or admission to hospital; **not** resulting in the prescription of systemic corticosteroids (tablets, suspension or injections – e.g. oral prednisone).*

A house is defined as:

- *A single building containing a single dwelling set on its own property. A house may contain a separate apartment or suite in the basement or attic.*

An apartment (or flat) is defined as:

- *A dwelling within a building comprising two or more individual dwellings (i.e. more flats or apartments).*

Questions to be asked at Visit 1 only:

For questions 1 and 2, please answer for the last 12 months only.

1. Has your child had a severe asthma attack (i.e. steroid tablets or liquid prescribed) in the last 12 months? Y / N

   If Yes - For the child's most recent severe asthma attack, how many days:

   a. Did the child miss from school? _____ days
   b. Did the child miss from work? _____ days
   c. Did you have to take off work to care for the child as a result of their asthma? _____ days
   d. Did somebody else have to take off work to care for the child as a result of their asthma? _____ days

2. Has your child had a non-severe asthma attack (i.e. steroid tablets or liquid not prescribed) in the last 12 months? Y / N

   If Yes - For the child's most recent non-severe asthma attack, how many days:

   a. Did the child miss from school? _____ days
   b. Did the child miss from work? _____ days

c. Did you have to take off work to care for the child as a result of their asthma? _____ days
d. Did somebody else have to take off work to care for the child as a result of their asthma? _____ days

Questions to be asked at Visits 1, 3 and 5:

*Please answer the following questions in relation to the child in the current study and **their primary household**.*

3. What is your relationship to the child?
    a. Father
    b. Mother
    c. Other relative or guardian (please specify) _____
4. How many people are in the child's household, including the child? _____
5. Is the child's current home an apartment or house?
    a. Apartment
    b. House
6. How many bedrooms are there in the child's home? _____
7. Not counting the child included in the current study, how many people in the household have had a severe asthma attack over the past **6 months**? _____
8. Not counting the child included in the current study, how many people in the household have had a non-severe asthma attack over the past **6 months**? _____
9. In general, over the last **6 months**, how much worry or concern did the child's asthma cause you?
    a. None at all
    b. A little bit
    c. Some
    d. Quite a bit
    e. A lot
10. In general, over the last **6 months**, were you limited in the amount of time you had for your own needs because of the child's asthma?
    a. Yes, limited a lot
    b. Yes, limited some
    c. Yes, limited a little
    d. No, not limited
    e. Don't know
11. In general, over the last **6 months**, has the child's asthma had any impact on decisions you have made regarding your participation in paid employment?
    a. Yes, a large impact
    b. Yes, some impact
    c. Yes, a little impact
    d. No impact
    e. Don't know
12. Has anything been done to the child's home in the past **6 months** to reduce the potential for asthma attacks such as installing new heating, insulation or ventilation?
    a. Installed heating (Y/N)
    b. Installed insulation (Y/N)
    c. Installed ventilation (Y/N)
    d. Other _____

13. In which range is your household income?

    a. Less than $20,000
    b. $20,001 – $40,000
    c. $40,001 – $60,000
    d. $60,001 – $80,000
    e. $80,001 – $100,000
    f. Over $100,000
    g. Prefer not to answer

Ask Q14 only at Visit 1 and Visit 5:

14. Do you own the home you live in:

    a. If Yes - Given your current situation, how much would you be prepared to pay to improve your current home (for example, install or update heating, insulation, or ventilation) if you could be sure that the improvements would prevent all further asthma (and related) events for the child? _____

    b. If No - Given your current situation, how much extra rent per week would you be prepared to pay for improvements to your current home (for example, rent a home with better heating, insulation, or ventilation) if you could be sure that the improvements would prevent all further asthma (and related) events for the child? _____

22 APPENDIX C: INHALER EDUCATION

Inhaler technique and maintenance checklists

Metered-dose inhaler (MDI) technique with a spacer (Airflow Space Chamber Plus) will be assessed at visits 1, 3 and 5. Note, for participants being prescribed a Turbuhaler at visit 5, they will receive inhaler education appropriate to this device instead.

MDI with a spacer

1. Check the dose counter (Symbicort or Seretide inhalers only)	
2. Take off the cap	
3. Hold the inhaler upright and shake for 5 seconds	
4. Fit the inhaler upright into the spacer	
5. Put the mouthpiece between your teeth without biting and close your lips to form a good seal	
6. Hold spacer level and press down firmly on inhaler canister once	
7. Take 6 slow breaths in and out through your mouth. Do not remove the spacer from your mouth between breaths	
8. Repeat steps 5 to 7 for each extra dose needed	
9. Remove the spacer from your mouth	
10. Remove the inhaler from the spacer and replace the cap	
11. Rinse your mouth with water or clean your teeth after using a preventer inhaler or Symbicort to help prevent side effects	

MDI <u>without</u> a spacer

You should always try to use a spacer with your inhaler to receive the most benefit from the medicine. However, if you need to use your inhaler without a spacer:

1. Check the dose counter (Symbicort or Seretide inhalers only)	
2. Take off the cap	
3. Hold the inhaler upright and shake for 5 seconds	
4. Insert the upright inhaler mouthpiece into your mouth and close your lips to form a good seal	
5. At the beginning of a slow deep breath, breathe in through the inhaler and press down on the cannister once	
6. Breathe in fully, remove the inhaler from your mouth and hold your breath for ten seconds or as long is comfortable	
7. Breathe out gently through your nose	
8. Repeat steps 4 to 7 for each extra dose needed	
9. Replace the cap on your inhaler when you are finished	
10. Rinse your mouth with water or clean your teeth after using a preventer inhaler or Symbicort to help prevent side effects	

Looking after your inhaler

You should clean your inhalers weekly to stop them from getting blocked.

1. Remove the cap from the mouthpiece and the metal canister (do not put the cannister in water)	
2. Rinse the mouthpiece and cap under warm water for at least 30 to 60 seconds	
3. Shake off excess water and leave the mouthpiece and cap to dry (overnight is recommended).	
4. Put the metal canister back in, and replace the cap	

If you need to use your inhaler before it is dry:

1. Shake off any excess water from the plastic casing and put the metal canister back inside	
2. Test spray the inhaler by firing two puffs into the air (away from your face)	

Looking after your Airflow Space Chamber Plus spacer

You should wash your spacer once a week with warm water and dishwashing liquid. Do not clean in the dishwasher.

1. Take the spacer apart by removing the bit where the inhaler sits	
2. Soak the parts for 15 minutes in warm water with dishwasher liquid	
3. Do not rinse. Shake off any excess water and leave to drip dry	
4. Reassemble the spacer	

Turbuhaler

1. Unscrew and remove the cover	
2. Hold the inhaler upright	
3. Twist the base anticlockwise and then back until you hear a click	
4. Breathe out, away from the Turbuhaler	
5. Place the mouthpiece in your mouth to form a seal with you lips	
6. Breathe in strongly and deeply. Remove the Turbuhaler and hold your breath for up to 10 seconds	
7. Replace the cover and twist to close	

23 APPENDIX D: ASTHMA ACTION PLANS

Budesonide-formoterol (Symbicort): Step 1

CARE
Children's Anti-inflammatory REliever

ASTHMA ACTION PLAN | SYMBICORT

Name: *Date of plan:*

GP: *GP phone:*

Study contact: *Study contact phone:*

Know your asthma symptoms

Know when and how to take your puffers

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 Symbicort

Remember...

- Take **2 puffs** of your **Symbicort** through a spacer when you wheeze, cough, or find it hard to breathe
- Take **2 puffs** of your **Symbicort** through a spacer if you find it hard to breathe when you exercise or play

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 6 puffs 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 puffer
- Take **2 puffs** of your **Symbicort** through a spacer 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 12 puffs of Symbicort a day
- **OR** you feel you need to see your doctor

Let's get help...

- **You need to go to the hospital or see your doctor today**
- Take **2 puffs** of your **Symbicort** through a spacer 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 16 puffs 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 **2 puffs** of **Symbicort** through a spacer, taking 6 breaths for each puff, as often as needed until help arrives
- Even if you seem to get better, seek medical help right away

Know your puffers

- The name of your puffer is **Symbicort**. The colour is **red**
- You take this puffer only when you need it
- You should **carry your Symbicort** with you at all times
- You should **always use a spacer** with your Symbicort and take **2 puffs** as needed to relieve symptoms

Study details...

Next appointment dates

Visit 2 _____

Visit 3 _____

Visit 4 _____

Visit 5 _____

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.

Budesonide-formoterol (Symbicort): Steps 2 and 3

CARE
Children's Anti-inflammatory Reliever

ASTHMA ACTION PLAN | SYMBICORT

Name: *Date of plan:*

GP: *GP phone:*

Study contact: *Study contact phone:*

Know your asthma symptoms

Know when and how to take your puffers

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 Symbicort

Remember...

Preventer and reliever: ***Symbicort***	___ *puffs(s) every morning*
	___ *puff(s) every night*
	2 *puffs 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 6 puffs 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 puffer
- Take **2 puffs** of your **Symbicort** through a spacer 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 12 puffs of Symbicort a day
- **OR** you feel you need to see your doctor

Let's get help...

- **You need to go to the hospital or see your doctor today**
- Take **2 puffs** of your **Symbicort** through a spacer 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 16 puffs 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 **2 puffs** of **Symbicort** through a spacer, taking 6 breaths for each puff, as often as needed until help arrives
- Even if you seem to get better, seek medical help right away

Know your puffers

- The name of your puffer is **Symbicort. The colour is red**
- Your Symbicort is both a preventer and a reliever puffer
- You take this everyday even when you are well, and when you need it
- You should **carry your Symbicort** with you at all times
- You should always use a spacer with your Symbicort

Study details...

Next appointment dates

Visit 2 _____

Visit 3 _____

Visit 4 _____

Visit 5 _____

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.

Budesonide-formoterol (Symbicort): Logbook (reverse side of action plan)

How to use your inhaler with a spacer

When using a metered dose inhaler (MDI), a spacer will help get the right dose of medicine into your lungs. Remember not to share your spacer with anyone else

1. Hold the inhaler upright and give it a good shake
2. Fit the inhaler into the opening at the end of the spacer
3. Seal lips firmly around the mouth piece, and press the inhaler once only
4. Take 6 slow breaths in and out through your mouth. Do not remove the spacer from your mouth between breaths
5. Remove the spacer from your mouth
6. Repeat steps 1-4 for further doses
7. Rinse your mouth with water or brush your teetch after using your Symbicort puffer

Washing your spacer

Wash your spacer once a week with warm water and dishwashing liquid.

Leave to drip dry (do not rinse). This will ensure that your medicine gets into your lungs and does not stick to the sides of the spacer

Since your last visit...

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

Start date	End date	How many days?	Did someone take time off work due to your asthma?	How many people took time off work due to your asthma? Who were they?	How many days did each person take off work?
e.g. 16/09/2020	*e.g. 18/09/2020*	*e.g. 3*	*e.g. Yes*	*e.g. 2 - me and mum*	*e.g. Me 2 days, Mum 1 day*

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

Medication started/changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Reason for medication
e.g. Amoxicillin	*e.g. 500mg*	*e.g. 3*	*e.g. 5 days*	*e.g. 15/09/2020*	*e.g. 20/09/2020*	*e.g. Sore throat*

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

Date	Type of visit	Was prednisone given?	Dose of Prednisone	How long for?	Start date	Stop date	Comments
e.g. 15/09/2020	*e.g. ED visit*	*e.g. Yes*	*e.g. 40mg*	*e.g. 4 days*	*e.g. 15/09/2020*	*e.g. 19/09/2020*	*e.g. Admitted*

Salbutamol (Ventolin): Step 1

CARE
Children's Anti-Inflammatory REliever

ASTHMA ACTION PLAN | VENTOLIN

Name: *Date of plan:*

GP: *GP phone:*

Study contact: *Study contact phone:*

	Know your asthma symptoms	Know when and how to take your puffers
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 Ventolin	**Remember...** • Take **2 puffs** of your **Ventolin** through a spacer when you wheeze, cough, or find it hard to breathe • Take **2 puffs** of your **Ventolin** through a spacer if you find it hard to breathe when you exercise or play
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 6 puffs a day, for one week	**Let's take action...** • You need to see your doctor within the next week to add a preventer puffer • Take **2 puffs** of your **Ventolin** through a spacer 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 Ventolin is only helping for 2-3 hours • **OR** you are using more than 12 puffs of Ventolin a day • **OR** you feel you need to see your doctor	**Let's get help...** • **You need to go to the hospital or see your doctor today** • Take **2 puffs** of your **Ventolin** through a spacer 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 Ventolin is not helping • **OR** you are using your Ventolin every 1-2 hours • **OR** you are using more than 16 puffs 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 **6 puffs** of **Ventolin** through a spacer every 6 minutes with 6 breaths for each puff until help arrives • Even if you seem to get better, seek medical help right away

Know your puffers

- The name of your reliever puffer is **Ventolin**. The colour is **blue**
- You take this puffer only when you need it
- You should **carry your Ventolin** with you at all times
- You should **always use a spacer** with your Ventolin and take **6 breaths** for each puff

Study details...

Next appointment dates

Visit 2 _____

Visit 3 _____

Visit 4 _____

Visit 5 _____

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.

Salbutamol (Ventolin): Step 1 logbook (reverse side of action plan)

How to use your inhaler with a spacer

When using a metered dose inhaler (MDI), a spacer will help get the right dose of medicine into your lungs. Remember not to share your spacer with anyone else

1. Hold the inhaler upright and give it a good shake
2. Fit the inhaler into the opening at the end of the spacer
3. Seal lips firmly around the mouth piece, and press the inhaler once only
4. Take 6 slow breaths in and out through your mouth. Do not remove the spacer from your mouth between breaths
5. Remove the spacer from your mouth
6. Repeat steps 1-4 for further doses

Washing your spacer

Wash your spacer once a week with warm water and dishwashing liquid.

Leave to drip dry (do not rinse). This will ensure that your medicine gets into your lungs and does not stick to the sides of the spacer

Since your last visit...

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

Start date	End date	How many days?	Did someone take time off work due to your asthma?	How many people took time off work due to your asthma? Who were they?	How many days did each person take off work?
e.g. 16/09/2020	*e.g. 18/09/2020*	*e.g. 3*	*e.g. Yes*	*e.g. 2 - me and mum*	*e.g. Me 2 days, Mum 1 day*

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

Medication started/changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Reason for medication
e.g. Amoxicillin	*e.g. 500mg*	*e.g. 3*	*e.g. 5 days*	*e.g. 15/09/2020*	*e.g. 20/09/2020*	*e.g. Sore throat*

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

Date	Type of visit	Was prednisone given?	Dose of Prednisone	How long for?	Start date	Stop date	Comments
e.g. 15/09/2020	*e.g. ED visit*	*e.g. Yes*	*e.g. 40mg*	*e.g. 4 days*	*e.g. 15/09/2020*	*e.g. 19/09/2020*	*e.g. Admitted*

Salbutamol (Ventolin): Steps 2 and 3

CARE
Children's Anti-inflammatory REliever

ASTHMA ACTION PLAN | VENTOLIN

Name: *Date of plan:*

GP: *GP phone:*

Study contact: *Study contact phone:*

Know your asthma symptoms

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 Ventolin

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 6 puffs a day, for one week

Feeling worried

Your asthma is a worry when...

- You are breathing fast or find it hard to breathe
- **OR** your Ventolin is only helping for 2-3 hours
- **OR** you are using more than 12 puffs of Ventolin a day
- **OR** you feel you need to see your doctor

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 Ventolin is not helping
- **OR** you are using your Ventolin every 1-2 hours
- **OR** you are using more than 16 puffs a day

Know when and how to take your puffers

Your inhalers are...

Preventer:	___	*puffs(s) every morning*
	___	*puff(s) every night*
Reliever: ***Ventolin***	**2**	*puffs when needed to relieve symptoms*

Let's take action...

- You need to see your doctor within the next week to change your preventer puffer
- Take **2 puffs** of your **Ventolin** through a spacer as often as needed to relieve symptoms

Let's get help...

- **You need to go to the hospital or see your doctor today**
- Take **2 puffs** of your **Ventolin** through a spacer as often as needed to relieve symptoms

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 **6 puffs** of **Ventolin** through a spacer every 6 minutes with 6 breaths for each puff until help arrives
- Even if you seem to get better, seek medical help right away

Know your puffers

- Preventer: You take this everyday even when you're well. The name of your preventer is _____. The colour is _____.
- Reliever: You take this only when you need it. The name of your reliever is **Ventolin**. The colour is **blue**
- You should **carry your Ventolin** with you at all times
- You should **always use a spacer** with your puffers

Study details...

Next appointment dates

Visit 2 _____

Visit 3 _____

Visit 4 _____

Visit 5 _____

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.

Salbutamol (Ventolin): Logbook for steps 2 and 3 (reverse side of action plan)

How to use your inhaler with a spacer

When using a metered dose inhaler (MDI), a spacer will help get the right dose of medicine into your lungs. Remember not to share your spacer with anyone else

1. Hold the inhaler upright and give it a good shake
2. Fit the inhaler into the opening at the end of the spacer
3. Seal lips firmly around the mouth piece, and press the inhaler once only
4. Take 6 slow breaths in and out through your mouth. Do not remove the spacer from your mouth between breaths
5. Remove the spacer from your mouth
6. Repeat steps 1-4 for further doses
7. Rinse your mouth with water or brush your teetch after using your preventer puffer

Washing your spacer

Wash your spacer once a week with warm water and dishwashing liquid.

Leave to drip dry (do not rinse). This will ensure that your medicine gets into your lungs and does not stick to the sides of the spacer

Since your last visit...

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

Start date	End date	How many days?	Did someone take time off work due to your asthma?	How many people took time off work due to your asthma? Who were they?	How many days did each person take off work?
e.g. 16/09/2020	*e.g. 18/09/2020*	*e.g. 3*	*e.g. Yes*	*e.g. 2 - me and mum*	*e.g. Me 2 days, Mum 1 day*

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

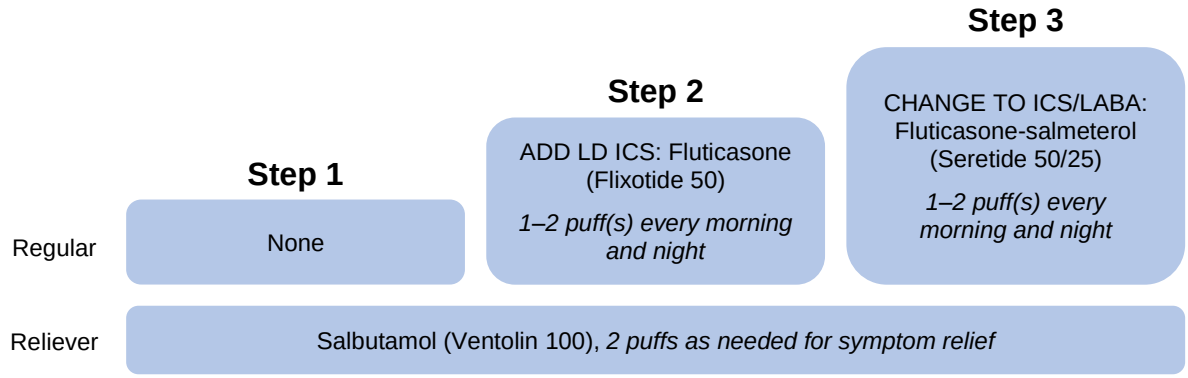
Medication started/changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Reason for medication
e.g. Amoxicillin	*e.g. 500mg*	*e.g. 3*	*e.g. 5 days*	*e.g. 15/09/2020*	*e.g. 20/09/2020*	*e.g. Sore throat*

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

Date	Type of visit	Was prednisone given?	Dose of Prednisone	How long for?	Start date	Stop date	Comments
e.g. 15/09/2020	*e.g. ED visit*	*e.g. Yes*	*e.g. 40mg*	*e.g. 4 days*	*e.g. 15/09/2020*	*e.g. 19/09/2020*	*e.g. Admitted*

24 APPENDIX E: CARE STEPWISE TREATMENT ALGORITHMS

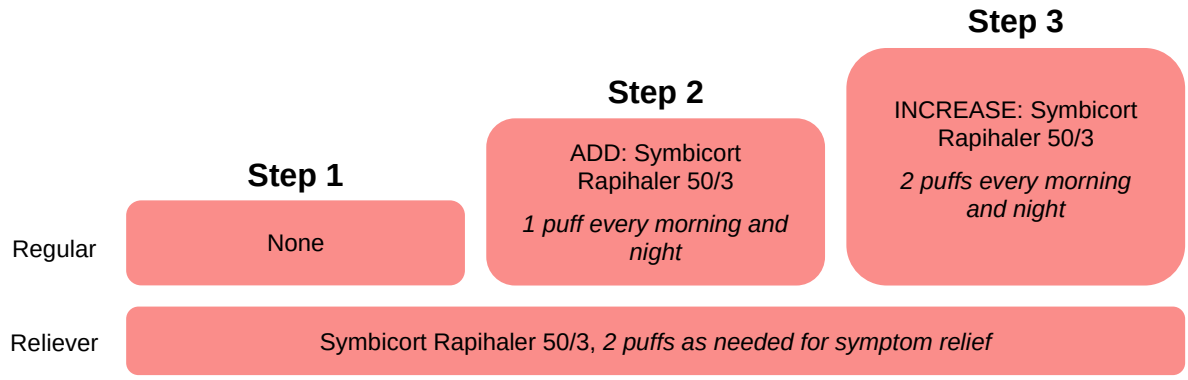
Control arm (Ventolin) algorithm



Treatment escalation in the control arm follows the NZ asthma guidelines (2017) for children and adolescents aged five to 15 years.[51]

Step 1	**Salbutamol (Ventolin) 100 two puffs as needed** NZ and international guidelines recommend that all children with asthma be prescribed a SABA reliever. Salbutamol pMDIs are the most commonly prescribed SABA inhalers in NZ (97% of SABA prescriptions in 2018).
Step 2	**Low-dose fluticasone propionate (Flixotide) twice daily, plus salbutamol (Ventolin) two puffs as needed** • Children aged 5 to 11 years will be prescribed fluticasone propionate 50mcg, 1 puff twice daily. • Children aged 12 to 15 years will be prescribed fluticasone propionate 50mcg, 2 puffs twice daily. Low-dose ICS has a marked beneficial effect on symptoms, lung function, and bronchial hyper-reactivity in children.[19,29,58] The dose-response curve for fluticasone in children plateaus between 100 and 200mcg per day for efficacy.[59] Fluticasone is the ICS of choice as it is available in a pMDI and the most commonly use ICS in children in NZ.
Step 3	**Low-dose fluticasone-salmeterol (Seretide) twice daily, plus salbutamol (Ventolin) two puffs as needed** • Children aged 5 to 11 years will be prescribed fluticasone-salmeterol 50/25, 1 puff twice daily. • Children aged 12 to 15 years will be prescribed fluticasone-salmeterol 50/25, 2 puffs twice daily. Maintenance low-dose ICS-LABA confirms greater symptom control and asthma attack risk reduction than doubling the ICS dose.[60–62] Fluticasone-salmeterol is the ICS-LABA of choice as it is available in a pMDI and offers an alternative ICS-LABA to budesonide-formoterol.

Intervention arm (Symbicort Rapihaler) algorithm



Treatment escalation in the intervention arm follows the principles outlined in the "anti-inflammatory reliever" approach for adults and adolescents, with age-adjusted doses.[63,64]

Step 1	**Very low-dose budesonide-formoterol (Symbicort Rapihaler) 50/3 two puffs as needed** The TREXA and ASIST trials demonstrated the safety and efficacy of as-needed Beclomethasone 50mcg with salbutamol 100mcg (separate inhalers) in children and adolescents aged five to 18 years.[30,31] Participants took two puffs of both inhalers as needed for symptomatic relief (total ICS/SABA doses per use of 100/200mcg respectively). Beclomethasone 50mcg is broadly equivalent to budesonide 50mcg, and formoterol fumarate 6mcg is equivalent to salbutamol 200mcg.[65–67] Beta-agonist doses are the same in adults and children. Total recommended daily ICS doses in children are half the doses in adults. Each as-needed use episode delivers the same beta-agonist dose as in adults using ICS-formoterol reliever therapy, but half the ICS dose (1 actuation of 200/6 vs 2 actuations of 50/3).
Step 2	**Very low-dose budesonide-formoterol (Symbicort Rapihaler) one puff twice daily, plus two puffs as needed** Bisgaard et al. demonstrated the safety and efficacy of Budesonide-formoterol MART in children aged four to 11 years using a dose of 100/6 (DPI) once daily and as needed:[35] • MART 100/6 once daily plus PRN reduced asthma attacks by 70% compared with budesonide 400mcg once daily. • Patients receiving MART grew significantly more than patients on fixed-dose budesonide (mean difference 1cm, 95% CI 0.3 to 1.7, p=0.0054). • The number of patients with abnormal pre–ACTH- and post–ACTH-stimulated plasma cortisol levels were similarly low in all groups (2/51 MART patients vs 1/55 fixed-dose ICS patients). The dose of ICS-formoterol 50/3 twice daily follows the principle of using the lowest dose of ICS to achieve good asthma control and minimise medication side effects.
Step 3	**Low-dose budesonide-formoterol (Symbicort Rapihaler) two puffs twice daily, plus two puffs as needed**

	Budesonide-formoterol MART at doses of 100/6 one puff twice daily, and 100/6 2 puffs once daily, improves asthma control in adolescents (12 to 17 years) compared to higher fixed-dose budesonide (400mcg daily).[34,68,69] There have been no studies of ICS-LABA MART at these doses in children aged 11 years and under. However, the Symbicort Turbuhaler 100/6 is approved for use in children aged four years and older at a standard maintenance dose of 1–2 actuations twice daily (maximum daily maintenance dose: 4 inhalations).[70] DPIs and pMDI are therapeutically equivalent. At step 3 of the BTS/SIGN 2019 asthma guidelines, a maintenance dose of budesonide-formoterol 100/6 twice daily is recommended in children aged 5 to 12 years.[71]

Recommended daily dose of ICS in children with asthma

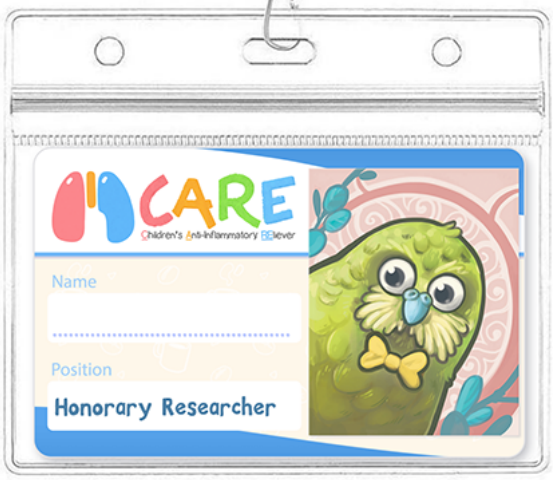
Recommended daily dose of ICS in children with asthma are:[51,71,72]

Steroid	Low dose	Standard dose	High dose
Beclomethasone dipropionate	200mcg/day	400 to 500mcg/day	800 to 1000mcg/day
Budesonide	200mcg/day	400mcg/day	800mcg/day
Fluticasone propionate	100mcg/day	200 to 250ncg/day	400 to 500mcg/day

25 APPENDIX F: PARTICIPANT ID BADGE AND STICKERS

Blank card

Card with sticker in example ID holder



Stickers

26 APPENDIX G: PARTICIPANT CERTIFICATE

27 APPENDIX H: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	V1.0	19/08/2020	N/A	N/A
1	V2.0	02/01/2020	RB, LH	Addition of secondary outcome "proportion of participants on each treatment step" and associated analysis Amended SABA use inclusion criterion to quantify use Section 12.5 and 12.7 – amended safety wording. Clarification of withdrawal, discontinuation, and lost to follow up criteria Updated Health Economics Questionnaire wording
2	V3.0	19/03/2021	RB, LH	Updated list of Investigators Extended asthma preventer medication use exclusion criterion (8.3.3) from 3 to 6 months Increased the minimum number of Ventolin inhalers dispensed at each visit from 2 to 3
3	V4.0	27/10/2021	RB, LH	Updated list of Investigators Provision for face-to-face visits to be done virtually and/or in-person (due to ongoing COVID-19 restrictions) FeNO, FEV1, Height, and Weight will not be measured at virtual visits Reimbursement to include covering internet/data costs Minor update to stickers to optimise for better readability at intended size and to meet printer specifications
4	V4.1	04/02/2022	RB, LH	Updated list of Investigators Reference to DCE sub-study (9.18) Added 13.3.2 to confirm a sensitivity analysis will be performed to check for effect modification between participants enrolled virtually versus in-person

5	V4.2	09/05/2022	RB, LH	Decreased the minimum number of reliever inhalers dispensed at each visit from 3 to 2.
6	V4.3	21/06/2022	RB, MH	Section 10.9 amended an error in the stated age groups for post-trial inhaler provision Section 16.6 updated text on reimbursement of participant expenses.
7	V5.0	08/05/2023	RB, MH	The planned sample size (section 3, Synopsis) and section 13.5.2 were updated to reflect the outcome of the interim sample size re-calculation, which resulted in the sample size being reduced from 380 to 360.