STATISTICAL ANALYSIS PLAN

Study 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)
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2 ADMINISTRATIVE INFORMATION

2.1 Protocol version

This document has been written based on information contained in the study protocol MRINZ/20/06 Version 5.1 (20/05/2024).

2.2 Author information

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3 STUDY DETAILS

3.1 Background and Rationale

A brief summary of the background and rationale for the study is found below. A more detailed rationale is found in the CARE study protocol.[1]

One in seven children in New Zealand have asthma, which accounts for more than 10% of all GP consultations for children and over 3000 hospital admissions annually.[2,3] Many children only use a short-acting beta$_2$-agonist (SABA) reliever inhaler, such as Ventolin. These inhalers provide fast symptom relief, but do not treat the underlying inflammation.

Two randomised controlled trials have compared as-needed budesonide-formoterol with as-needed SABAs in adults and adolescents with mild asthma.[4,5] Both studies demonstrated a significant reduction in asthma attacks with as-needed budesonide formoterol; asthma attacks (moderate and severe) were reduced by 51% (relative rate 0.49, 95% confidence interval [CI] 0.33 to 0.72) in the Novel START trial, and 60% (relative rate 0.40, 95% CI 0.32 to 0.49) in the SYGMA 1 trial, and severe asthma attacks were reduced by 57% (relative effect 0.43, 95% credible interval 0.33 to 0.72).[6] Budesonide-formoterol reliever therapy also 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.[4,7]

International recommendations for the management of asthma in adolescents and adults were changed in response to these findings, with the Global Initiative for Asthma (GINA) no longer recommending the use of unopposed SABAs in this patient population; ICS-formoterol is now the preferred reliever option across all asthma severities.[8] Whether these findings are relevant to childhood asthma is unknown as there have been no RCTs of the as-needed budesonide-formoterol regimen in children. If comparable efficacy of this regimen is shown in childhood asthma, then its implementation would transform international guideline recommendations and have the potential to markedly reduce asthma morbidity globally.

3.2 Objectives

3.2.1 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 attack count reported as rate per participant year	52

3.2.2 Secondary

3.2.2.1 To determine the *efficacy* of as-needed budesonide-formoterol compared with salbutamol.

Outcome Measure(s)	Time point (week)
2. Severe asthma attack count reported as rate per participant 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

3.2.2.2 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

3.2.2.3 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

3.3 Study design

The CARE study is an investigator-initiated, 52-week, New Zealand-based, 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 in-person; visits 2 and 4 will be conducted via telephone.

3.4 Randomisation

Randomisation was performed using a computer-generated sequence to maintain allocation concealment. Block size varied by site; sites anticipated to recruit larger numbers had 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 had a single block size of 48 per four level stratification variable, for a total of 192 randomisations per site. This was generated by the study statistician, independent of the Investigators.

If two or more participants from the same primary household are enrolled into the study, the first participant will be randomised as above; all subsequent members of the same primary household will then be allocated to receive the same treatment as the first member of the primary household. This strategy is to improve adherence to the randomised regimen.

Allocation concealment is by a secure database, which contained the randomisation sequence.

3.5 Sample size

Full details of the original sample size calculation and interim sample size calculation are in the CARE study protocol. An annualised asthma attack rate of 0.28 was determined from studies of ICS-SABA reliever therapy (separate inhalers) in children. The relative rate of attacks for budesonide-formoterol reliever therapy versus salbutamol reliever therapy in adults with mild asthma is between 0.40 and 0.49. We have chosen the sample size to detect a more conservative relative rate of 0.55. By simulation from appropriate Poisson distributions, we estimated 160 participants were needed in each group (a total recruitment of 320 participants) to detect a difference in rates between 0.28 in the active-treatment arm and 0.51 in the SABA-only arm, with 90% power, two-sided alpha of 5%. To account for dropouts, an additional 20% was added to give a total sample size of 380 participants (190 in each arm). An interim sample size re-estimation is planned for after 60% (n=228) of trial participants had been recruited.

3.6 Sample size re-estimation

A masked assessment of the rate of asthma attacks (primary outcome) in the two randomised arms is planned after 228 (60%) participants are recruited. The 95% CI will be estimated for the highest rate of asthma attacks, and used as the basis of a re-estimation for the sample size. This will still be based on detecting a relative rate of 0.55, using the upper and lower 95% confidence limits for the highest rate as the basis for the re-estimation. The number of participants recruited will be adjusted accordingly, resources permitting.

3.7 Interim safety statistical analysis

A Data and Safety Monitoring Committee (DSMC) will be established, chaired by a paediatric and perinatal epidemiologist and statistician at the University of Auckland, who is independent from the study team. The DSMC will review all serious adverse events and the results of the interim safety statistical analysis.

An interim safety statistical assessment and/or analysis of unplanned hospital admissions for asthma of ≥24 hours duration will be undertaken by the study statistician after 228 (60%) participants have been recruited. This analysis will be performed masked to treatment allocation; the data for assessment and/or analysis will be provided without the participant 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). 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 Trial Steering Committee (TSC) will make the final decision on whether or not to terminate the trial.

3.8 Timing of final analysis and timing of outcome assessments

All outcomes will be analysed collectively after completion of:

1. The last participant last visit (LPLV); and
2. Medical record reviews for all participants.

4 STATISTICAL PRINCIPLES

4.1 Confidence intervals and P values

For all outcomes this will be conducted as a superiority analysis. All applicable statistical tests will be two-sided and will be performed using a 5% significance level. All confidence intervals presented will be 95% and two-sided. There will be no formal adjustment for multiplicity and secondary outcome analyses will be treated as exploratory.

4.2 Adherence and protocol deviations

In order to more closely mimic clinical use in clinical practice, compliance with the intervention will be encouraged through participant education but it will not be recorded.

A protocol deviation is defined as failure to adhere to the protocol, such as the wrong intervention being administered, incorrect data being collected and documented, and errors in applying inclusion/exclusion criteria. Reasons for deviation will be categorised as:

- Enrolment of ineligible participant
- Study medication error e.g. supplying the participant with expired inhalers
- Participant not withdrawn in error
- Other (to be stated)

A potential participant who was randomised but who did not meet the inclusion and exclusion criteria will be deemed ineligible, and not included as part of the intention to treat analysis data set. On occasions a participant may only be identified as ineligible during follow up. If this is the case no measurements from the ineligible participant will be included in the intention to treat data set.

Reasons for deviations will be summarised as above, for each treatment group. Other minor deviations from protocol (not affecting the study results) may be recorded during the study. These will not be formally presented either to the DSMC or in the final report, however they will be checked and recorded as part of study monitoring.

The number (and proportion) of participants with protocol deviations and protocol violations will be summarised by treatment group with details of the type of deviation provided. The participants that are included in the safety dataset will be used as the denominator to calculate the proportions.

A protocol violation is defined as one affecting the efficacy, safety, physical or mental integrity of the participants in the trial, or the scientific value of the trial.

4.3 Analysis populations

4.3.1 Intention-To-Treat Analysis dataset

The intention-to-treat analysis dataset for the primary analysis will include all participants according to the treatment they were randomised to receive unless, as described above, potential participants were actually ineligible, and so randomised in error.

Data will be collected for the intention to treat data set until completion of the study or withdrawal from the study. If a participant is on a course of oral corticosteroids at the point of withdrawal then the whole course of oral corticosteroids will be recorded for calculation of oral corticosteroid use.

No data collection is planned after withdrawal of consent for continued collection of data. Data imputation will not be used for those who withdraw from the study before the planned completion date because it cannot be assumed that their subsequent data will be missing completely at random or missing at random.

For the purpose of adverse event reporting and analysis, the safety analyses will include all participants who are dispensed randomised study medication at Visit 1.

4.3.2 Per-Protocol Analysis dataset

The per-protocol analysis dataset for the secondary analysis will include participants who completed treatment per protocol. Participants who discontinued treatment will be excluded from this analysis as will participants involved in a protocol violation deemed to affect the integrity of the study data.

4.4 Data description for outcome variables

Categorical data will be summarised by counts and proportions expressed as percentages. Continuous data will be summarised by mean, standard deviation, median, interquartile range, and range (minimum to maximum). Full summary data for continuous variables will be reported irrespective of whether analyses based on normal distribution assumptions are used or not.

5 TRIAL POPULATION

5.1 Screening data

A CONSORT diagram will be used to report enrolment and withdrawal data in line with CONSORT guidelines.

5.2 Discontinuation

The CONSORT diagram will report the primary reason for discontinuation as one of the following:

- Uncontrolled asthma resulting in safety concerns, as judged by the investigator
- The participant and/or their parent/guardian withdrew consent/assent for participation and data collection
- The participant withdrew due to an AE
- Participant decision for reasons other than withdrawal due to an AE:
    - Asthma related
    - Not asthma related
- The participant became pregnant
- Any safety reason (not including uncontrolled asthma resulting in safety concerns) as judged by the investigator (to be stated)
- The participant was lost to follow up
    - Those who were lost to follow up after the baseline visit (visit one) and provided no follow up data at all
    - Those who were lost to follow up and provided some follow up data
- Sponsor decision (to be stated)
- Other (to be stated)

5.3 Baseline participant characteristics

Baseline characteristics are: height, weight, BMI, sex, ethnicity, age (years), age group (≤11 years, ≥12 years), age at diagnosis, ACQ-5 score, whether prescribed ICS in the 12 months prior to enrolment, whether ever previously prescribed an ICS, self-reported SABA use in last 4 weeks, proportion with SABA use >2 occasions per month, on treatment FEV1 % predicted, on treatment FEV1 z-score, FeNO (ppb), severe asthma attack in the past 12 months, number of severe asthma attacks in the past 12 months in those that had at least one, ED attendance for asthma in the last 12 months, hospital admission for asthma ever, pre-study ownership of a written asthma self-management plan, smoking status and pack years, e-cigarette use (vaping) status, household smoking exposure, history of atopy, and first degree relative with asthma.

Differences in the distribution of baseline variables by randomised treatment will not be tested statistically. However, important co-variates will be included in sensitivity analyses as outlined below, without respect to statistical evidence of different distributions by randomisation status.

Baseline characteristics of participants who were lost to follow up following visit 1, and so provided no follow up data, will be summarised in an additional table within the supplementary appendix.

6 STATISTICAL ANALYSIS

6.1 Definition of terms

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) but not severe enough to warrant the prescription of systemic corticosteroids (e.g. oral prednisone) or hospital admission.

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).

An ***asthma attack*** encompasses both moderate and severe asthma attacks.

Determining asthma attack status:

- Urgent, unplanned medical reviews are consultations with a healthcare provider (e.g. GP, ED doctor, paramedic, or nurse practitioner) to review worsening asthma, that were not routinely scheduled before the asthma worsened. These reviews may be done in-person and/or remotely (e.g. by telephone). Pre-planned, routine asthma reviews or check-ups do not count as urgent reviews.

- The start date of an asthma attack is the date of the first urgent, unplanned medical review for the event. The start date of a severe asthma attack is the date of the first prescription of systemic corticosteroids for the event.

- 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.

- For an attack to be counted as a separate event, there must be more than seven days between healthcare encounters. For example:

    - Two urgent reviews for worsening asthma within a seven-day period should be recorded as part of the same asthma attack.

    - Two urgent reviews for worsening asthma separated by seven or more days should be recorded as two separate asthma attacks.

    - One urgent review for worsening asthma followed by a scheduled follow up (any time frame) should be recorded as one asthma attack (the “scheduled follow up” does not meet the criteria for an “urgent, unplanned medical review”).

- Worsening asthma may be confirmed by documentation of a respiratory illness associated with increased wheezing and/or increased reliever use and/or recognition of worsening ‘asthma’.

- Prescription of systemic corticosteroids, regardless of participant use, defines whether an asthma attack is severe or not. This includes delayed scripts/prescriptions for systemic corticosteroids.

- If a participant is prescribed a course of systemic corticosteroids for later use in the event that their current asthma attack worsens, or in the event of a future attack, then this would meet the criteria of a severe asthma attack.

- If on planned (non-acute) medical review a participant is prescribed a course of systemic corticosteroids, for use in the event of a future attack, then this would not meet the criteria of a severe asthma attack.

- If a course of systemic corticosteroids is dispensed by a study investigator, in the situation for example of a GP not being available in the situation of worsening asthma, then this scenario would not meet the criteria of a moderate or severe asthma attack.

- If a participant took a course of systemic corticosteroids, from a home supply, without medical review for the index attack, then this scenario would not meet the criteria of a moderate or severe asthma attack.

- If on medical practitioner review, a diagnosis of asthma attack was not confirmed, but the adjudication committee consider there is clear documentation that the participant presented with a respiratory illness associated with worsening asthma, then it would be confirmed as a moderate or severe attack, depending on whether systemic corticosteroids were prescribed.

6.2 Outcome definitions

The outcome(s) designated with an asterisk (*) will not be reported in the main manuscript and its supplementary appendix.

6.2.1 Primary outcome

The primary analysis of the primary outcome variable, the count of asthma attacks (moderate and severe) in relation to the time of observation in the study, will be by estimation of the relative rate of asthma attacks per participant year.

6.2.2 Secondary outcomes

6.2.2.1 Efficacy

- Severe asthma attack count as rate per participant year
- Proportion of participants with at least one asthma attack
- Proportion of participants with at least one severe asthma attack
- Proportion of participants on each treatment step
- Time to first asthma attack
- Time to first severe asthma attack
- Days in hospital
- Fractional Exhaled Nitric Oxide (FeNO)
- On-treatment Forced Expiratory Volume over 1 second (FEV1)
- Asthma Control Questionnaire 5 (ACQ-5)
- Days lost from school due to asthma
- Days lost from work due to asthma (participant)
- Days lost from work due to childcare for asthma (parent(s)/guardian(s)

6.2.2.2 Safety

- Total systemic corticosteroid dose
- Growth velocity
- Adverse Events
- Serious Adverse Events

6.2.2.3 Cost-effectiveness

- Net cost per asthma attack prevented*

6.3 Missing data

In order to minimise missing data, data will continue to be collected from participants if their treatment is changed/they are discontinued from the randomised treatment regimen. Data for withdrawals will be collected until the date of withdrawal. Participants will only be considered "withdrawn" from the study if they actively rescind their consent/assent to the continued collection of data. Data collected up until the date of withdrawal will be included in the analysis (Table 1).

Discontinuation/Withdrawal type	
Discontinuation from randomised treatment only	• Continue study procedures/visits and ongoing data collection (participants and medical records). • Data for the full 52-week period will be included in the analysis.
Discontinuation from randomised treatment *and* study procedures/visits (withdrawal)	• Data collected for the period between date of enrolment and date of withdrawal will be included in the analysis. • No further data will be collected after the date of withdrawal.
Lost to follow-up	• To be applied retrospectively at week 52 to the date of last participant contact. Data collected for the period between date of enrolment and date of lost to follow-up will be included in the analysis.

Table 1: Statistical analysis options following discontinuation/withdrawal.

All participants provide their National Health Index (NHI) number on enrolment. If available at completion of the study, this will be used to review prescription and hospital discharge data via the Ministry of Health's National Minimum Dataset (NMD).

Sites and the Sponsor via sites may also need to access a participant's primary care medical record to clarify incomplete, associated or missing data (e.g. for asthma attacks) during their time in study.

Self-reported data, medical record data, and data from national datasets (where available) will be reviewed together; discrepancies will be arbitrated using predefined criteria:

- All self-reported exacerbations will be included in the analysis datasets, regardless of whether there is prescription or hospital admission data present for this event in the NMDS.

- New exacerbations can be added to the analysis datasets where prescription or hospital admission data indicate an asthma exacerbation occurred (i.e. admission for asthma or script for prednisone for asthma, where there was no prior self-report). Primary care and/or hospital records may need to be reviewed to help validate such an event. This may result in the addition of new, not previously reported AEs/ SAEs.

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.

6.4 Additional data

Data from additional time in study beyond the planned 365-day participant enrolment period will be included in the final analysis even where there is a significant delay in study completion. For variables that do not explicitly include time (i.e. those other than rate or time to first event), a sensitivity analysis will be performed with a cut point of 456 days post-randomisation (i.e. 365 day intended study enrolment plus 91 days [13 weeks]).

6.5 Analysis methods

6.5.1 Primary outcome variable analysis

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

A sensitivity analysis will include the following potentially important predictors of response: age, sex, ethnicity, baseline ACQ score, trial site, 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 be considered as a dichotomous variable split by age group (five to 11 years; and 12 to 15 years).

A sensitivity analysis will be undertaken for the primary outcome variable which includes all courses of systemic corticosteroids, either prescribed, dispensed or taken, for a respiratory illness associated with increased wheezing and/or increased reliever use and/or recognition by the participant/family as ‘worsening asthma’. This may include events such as use of systemic corticosteroids taken from a home supply without review from a GP, a backpocket prescription for use if the asthma attack worsened further, and a course of systemic corticosteroids dispensed by an investigator in the situation of a GP not being available.

The number of moderate and severe exacerbations by healthcare encounter type (GP, After Hours, ED, hospital admission and ‘other’ such as ambulance service) will be reported.

6.5.2 Secondary outcome variable analyses

The following methods will be used:

6.5.2.1 Poisson regression with an offset for the time of observation and a fixed effect of randomised treatment allocation:

- Severe asthma attack count per participant 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.

6.5.2.2 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 at completion of study
- 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.

6.5.2.3 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

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

- FEV_1 mL
- FEV_1 z-score
- FEV_1 % predicted
- FeNO (on the logarithm-transformed scale)
  - A sensitivity analysis will be performed to compare results obtained from NIOX VERO vs FeNObreath devices.*
- Growth velocity

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

- ACQ-5

6.5.2.6 Analysis dependent on data distribution:

* FeNO testing was initially performed with FeNOBreath devices, however due to technical and supply issues, the trial management group approved a change to NIOX Vero devices. Each participant used the same type of device for the duration of their time in study.

- Total oral corticosteroid dose (as prednisolone equivalent)

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.

6.5.2.7 Baseline cost-effectiveness analysis

- See separate economic analysis plan.

6.6 Treatment effect modification

To explore if baseline characteristics are associated with treatment response, sub-group analyses will be performed for three outcome variables: rate of asthma attacks, rate of severe asthma 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 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
- Smoking status
- Household smoking status
- Baseline ACQ-5 score (for asthma attacks and severe asthma attacks outcomes only)
- Baseline FeNO
- Baseline FEV1 % predicted

For illustration on the Forest Plot, baseline ACQ-5 score, baseline FeNO, and baseline FEV1 % predicted will be dichotomised at the median value of the control arm.

Whether there is evidence of a sub-group effect will be tested by fitting interaction terms between treatment and the possible effect modifying variables for the three selected outcome variables. For the rate of asthma attacks, and the rate of severe asthma attacks, we plan to use Poisson regression, with an offset for the time of observation. Dependent on the data distribution for the asthma attacks and severe asthma attacks, this may be better modelled as logistic regression if there are very few asthma attacks. ACQ-5 will be modelled with ANCOVA.

6.7 Harms

Adverse events (AEs) and serious adverse events (SAEs) will be systematically captured during the study as described in the protocol (section 12). The number (%) of AEs by system organ class will be reported by treatment group. The most common AEs (occurring in ≥2% of patients) will be reported for patients with at least one AE. Patients with at least one SAE (including death) will be reported by treatment group. The number (%) of SAEs by preferred term will be reported by treatment group.

6.8 Statistical software

SAS version 9.4 will be utilised, however should there be a requirement for a different version or different program to analyse particular variables or data then this will be specified in the statistical analysis report.

6.9 Data management plan

Data management will be in accordance with the CARE Data Management Plan.

7 SECONDARY ANALYSES

The following secondary analyses will be reported in separate manuscripts. Unless otherwise specified, data will be handled as for the primary analyses.

7.1 Ethnicity analysis

Differences in outcome relating to ethnicity will be assessed using an interaction term between ethnicity and treatment. In addition, comparison will be made for the subgroups of:

- Māori vs 'Asian/European/Other'; and
- Pacific peoples vs 'Asian/European/Other'

The primary outcome measure will be rate of asthma attacks per person per year. Additional outcomes will include rate of severe asthma attacks per participant per year, time to first asthma attacks, time to first severe asthma attack, ACQ-5, on treatment FEV1, FeNO, proportion of participants withdrawn and reason, adverse events, and serious adverse events. Data analysis will be by intention to treat.

The general analysis strategy will be to test an ethnicity-treatment interaction term for each outcome variable. If this is significant, $P<0.05$, we plan to report the difference between as-needed ICS-formoterol use and as-needed SABA use for Māori and Asian/European/Other', and for Pacific peoples and Asian/European/Other' separately. If the interaction term is not statistically significant, consistent with the relative effect of treatment being the same in Māori and Asian/European/Other', and for Pacific peoples and Asian/European/Other' we plan to report the difference in outcome for Māori and Asian/European/Other', and for Pacific peoples and Asian/European/Other', adjusted for treatment, and the difference between treatments, adjusted for ethnicity.

7.2 Predictive models of asthma attacks

The predictive value of (1) FeNO, (2) ACQ-5, (3) FEV_1 (percent predicted) and (4) history of a severe asthma attack ≤12 months (alone and in combination) on future asthma attack and severe asthma attack risk, in children with mild asthma, will be explored.

Participants will be analysed separately according to randomised treatment arm.

Cox's proportional hazards and regression survival analysis illustrated by Kaplan-Meier plots will be used to estimate the hazards for asthma attacks (moderate and severe) and severe asthma attacks in relation to the following variables at week 0 (baseline):

1. FeNO
2. ACQ-5
3. FEV_1 (percentage predicted)
4. History of at least one severe asthma attack ≤12 months.

Receiver operator curves in logistic regression will be used to estimate the sensitivity and specificity at prespecified boundaries (e.g. 1 week, 1 month, 3 months, 6 months, 12 months).

Multivariate regression will be used to explore the predictive value of multiple measures (e.g. FeNO and ACQ-5 in combination).

Sensitivity analyses will explore the interaction between randomised treatments (salbutamol or budesonide-formoterol), age group (<11 / 12+), sex (male or female), and ethnicity (Asian, European, Māori, Pacific, Other), device (FeNObreath or NIOX Vero) and the predictive value against established cut points for FeNO (<20, 20 – 35, >35) and ACQ-5 (<0.75, 0.75 – 1.5, >1.5), and dichotomised cut points for FEV1 (<80% predicted / ≥80% predicted) and history of at least one severe asthma attack ≤12 months (0 or ≥1)

7.3 Intermittent vs mild persistent asthma

This secondary analysis will explore differences in treatment effect between “intermittent asthma” and “mild persistent asthma”.

- Intermittent asthma: use of SABA-alone on ≤2 occasions/week in the four weeks prior to study entry and no severe asthma attack in the previous year.
- Mild persistent asthma: use of SABA-alone on >2 occasions/week in the four weeks prior to study entry, and/or ≥1 severe asthma attack in the previous year.

The associations between asthma attacks, randomised treatment and intermittent vs persistent subgroup will be analysed by Poisson regression with an offset for time in study, severe exacerbations by logistic regression, and Asthma Control Questionnaire (ACQ)-5 by analysis of covariance with baseline value as continuous covariate. Interaction terms between treatment and subgroup evaluated differences between subgroup responses. There will be no adjustment for multiple analyses.

7.4 Combined analysis

We plan to undertake a combined analysis of data from this study and other RCTs of budesonide/formoterol reliever therapy regimens. The statistical methodology for these analyses will be reported for each specific study.

8 DISCRETE CHOICE EXPERIMENT ANALYSIS

Preference weights will be calculated for each participant. Preference weights will also meaned for all child participants and all parent/guardian participants. Continuous variables are described by mean and standard deviation or median and interquartile range. Categorical variables are described by counts and proportions as percentages. Sensitivity analyses will be performed to check for effect modification of randomised treatment regimens (PRN ICS-LABA vs PRN SABA), between participants with a personal or household history of an asthma attack requiring an urgent medical review, or not, and between those who completed the DCE virtually versus in-person.

9 REFERENCES

1. Hatter L, Bruce P, Holliday M, et al. The Children's Anti-inflammatory REliever (CARE) study: a protocol for a randomised controlled trial of budesonide-formoterol as sole reliever therapy in children with mild asthma. *ERJ Open Res*. Published online January 1, 2021:271-2021. doi:10.1183/23120541.00271-2021

2. Barnard L, Zhang J. The impact of respiratory disease in New Zealand: 2020 update. *Asthma and Respiratory Foundation NZ*. Published online 2021.

3. Dowell A, Darlow B, MacRae J, Stubbe M, Turner N, McBain L. Childhood respiratory illness presentation and service utilisation in primary care: A six-year cohort study in Wellington, New Zealand, using natural language processing (NLP) software. *BMJ Open*. 2017;7(7):1-9. doi:10.1136/bmjopen-2017-017146

4. Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *New England Journal of Medicine*. 2019;380(21):2020-2030. doi:10.1056/NEJMoa1901963

5. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma. *New England Journal of Medicine*. 2018;378(20):1865-1876. doi:10.1056/NEJMoa1715274

6. Rogliani P, Ritondo BL, Ora J, Cazzola M, Calzetta L. SMART and as-needed therapies in mild to severe asthma: a network meta-analysis. *European Respiratory Journal*. Published online 2020. doi:10.1183/13993003.00625-2020

7. Pavord ID, Holliday M, Reddel HK, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. *Lancet Respir Med*. Published online 2020. doi:10.1016/s2213-2600(20)30053-9

8. Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J*. 2019;53(6). doi:10.1183/13993003.01046-2019

10 APPENDIX A: AMENDMENT HISTORY

Amendment no.	Protocol version	Updated SAP version no.	Description of and reason for change	Date changed