Protocol for the INFORM ASTHMA Trial: budesonide–formoterol reliever in adults with asthma on maintenance inhaled corticosteroid

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Shareable abstract (@ERSpublications)
This protocol describes the INFORM ASTHMA Trial, the first RCT comparing the anti-inflammatory action, efficacy and safety of ICS/formoterol *vs* SABA reliever in adults on maintenance ICS, providing crucial evidence for a common asthma therapeutic regimen https://bit.ly/3C9dOEq

Cite this article as: Noble J, Bean O, Bruce P, *et al*. Protocol for the INFORM ASTHMA Trial: budesonide–formoterol reliever in adults with asthma on maintenance inhaled corticosteroid. *ERJ Open Res* 2025; 11: 01208-2024 [DOI: 10.1183/23120541.01208-2024].

Received: 7 Nov 2024
Accepted: 2 Jan 2025

Abstract

Background International asthma guidelines recommend inhaled corticosteroid (ICS)/formoterol in preference to short-acting β_2-agonist (SABA) reliever-based regimens as reliever therapy in adults and adolescents of all asthma severities. A major limitation to this recommendation is the absence of randomised controlled trial (RCT) efficacy and safety data for this approach in patients who continue to use maintenance ICS. The anti-inflammatory effect of ICS/formoterol reliever therapy on airway inflammation is also not well characterised.

Objective The objective of the present study is to determine the anti-inflammatory effect, efficacy and safety of budesonide–formoterol reliever therapy *versus* terbutaline reliever therapy in adults with asthma on maintenance ICS therapy. Fractional exhaled nitric oxide (F_{ENO}) will specifically be examined to determine the time-course and magnitude of the anti-inflammatory effect.

Methods A 26-week, open-label, parallel-group, 2-arm, phase IV, two-sided superiority RCT will recruit 180 adults aged 16–75 years with a clinical diagnosis of asthma using reliever only therapy, or SABA reliever therapy with maintenance ICS at baseline, and with baseline F_{ENO} at screening $\geqslant$25 ppb. Enrolled participants will be allocated to maintenance budesonide with the dose based on their baseline treatment step and randomised 1:1 to either budesonide–formoterol or terbutaline reliever therapy. All participants will perform at-home F_{ENO} measurements at regular intervals for the first 12 weeks of the study. The primary outcome is F_{ENO} at 26 weeks. Key secondary outcomes include F_{ENO} time-course, asthma exacerbations, asthma control and spirometry.

Conclusion This will be the first RCT comparing ICS/formoterol *versus* SABA reliever therapy in patients who use maintenance ICS therapy.

Introduction

This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 recommendations [1, 2]. Headings and subheadings have been annotated to correspond to the item number in the SPIRIT 2013 checklist. Administrative Information (SPIRIT items 1 to 5) is detailed in table 1.

Background and rationale (item 6)

Asthma is a chronic inflammatory airways disease, characterised by variable airway obstruction that manifests clinically in episodic symptoms. For decades, asthma not controlled with as-needed short-acting

TABLE 1 Administrative information, as per sections 1–5 in the SPIRIT 2013 Checklist [1]

Section	Description
Title	The randomised controlled trial of budesonide–formoterol *versus* terbutaline for symptom relief in adults with mild–moderate asthma trial (INFORM ASTHMA Trial)
Trial registration	Australian New Zealand Clinical Trials Registry reference ACTRN12622001304729
Protocol version	The protocol version at the time of publication is version 3.4, dated 12 October 2023
Funding	The INFORM ASTHMA Trial has received funding and supply of study medication from AstraZeneca through their externally sponsored research pathway (reference ESR-23-22270)
Roles and responsibilities	J. Noble, O. Bean, P. Bruce, M. Black, B. Black, M. Holliday and R. Beasley designed the study. J. Noble, O. Bean, M. Black, B. Black, M. Holliday, R. Sayers, R. Cullen, L. Kirton and B. Perry are conducting the study. I. Pavord, A. Eathorne and M. Weatherall are responsible for designing and conducting the statistical analyses The study is sponsored by the Medical Research Institute of New Zealand (MRINZ): richard.beasley@mrinz.ac.nz The MRINZ designed the study, wrote the protocol and is responsible for all study-related activities including collection, management and analysis of study data, its interpretation and decision to submit reports for publication AstraZeneca had no role in the design of the study or in writing the study protocol. They will have no role in collection, management or analysis of study data and will have no role in the decision to submit study manuscripts for publication

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trial; MRINZ: Medical Research Institute of New Zealand.

β_2-agonists (SABAs) has been treated with regular daily maintenance inhaled corticosteroid (ICS). The Global Initiative for Asthma (GINA) guidelines recommend an escalation of daily ICS dose, with or without additional long-acting β_2-agonist (LABA) add-on therapy, in a stepwise manner to achieve asthma control [3].

The GINA guidelines changed significantly in 2019 [4]. Instead of as-needed SABA-based regimens, they recommended combination ICS/formoterol as the preferred reliever therapy in adolescents and adults, for all severities of asthma, with or without maintenance ICS/formoterol [5–7]. However, a major limitation to the recommendation of ICS/formoterol reliever-based regimens is the absence of evidence for the safety and efficacy of ICS/formoterol reliever therapy in those that are prescribed maintenance ICS. Worldwide, maintenance ICS is the most common form of maintenance therapy for asthma [8], and so this represents a significant gap in the evidence-base for a common treatment regimen.

We plan to address this knowledge gap by conducting the first randomised controlled trial (RCT) of ICS/formoterol reliever *versus* SABA reliever therapy in patients that also take daily maintenance ICS. This provides the opportunity to expand the evidence for the time-course and magnitude of anti-inflammatory effects of ICS when titrated through bronchodilator reliever use, a key mechanism of action for ICS/formoterol reliever therapy [9], examined through measuring the effects of reliever therapy on fractional exhaled nitric oxide (F_{ENO}), a validated marker of Type 2 (T2) inflammation in asthma and a key treatable trait in airways disease [10–12].

Objectives (item 7)

The objective is to determine the anti-inflammatory action, efficacy and safety of budesonide–formoterol reliever therapy compared to terbutaline reliever therapy in adults with asthma treated with maintenance ICS therapy.

Study design (item 8)

The randomised controlled trial of budesonide–formoterol *versus* terbutaline for symptom relief in adults with mild–moderate asthma trial (INFORM ASTHMA Trial) is a 26-week, open-label, parallel-group, two-arm, phase IV, two-sided superiority RCT.

Methods

Participants, interventions and outcomes

Study setting (item 9)

The study will be conducted in three New Zealand sites operated by the Medical Research Institute of New Zealand (MRINZ) (supplementary table S1).

Eligibility criteria (item 10)

Eligibility criteria (table 2) will be formally assessed at the first study visit prior to randomisation. Participants must have a doctor-diagnosis of asthma and use either reliever therapy only, or maintenance

TABLE 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Self-reported doctor's diagnosis of asthma for ⩾6 months prior to Visit 1	Current use (within the last 3 months) additional asthma therapies including:
Age 16 to 75 years at Visit 1	Maintenance ICS/LABA
Current use (within the last 3 months) of either:	Leukotriene receptor antagonists
Reliever only therapy, including SABA and/or ICS/LABA or	Oral maintenance theophylline
ICS maintenance (any dose) plus SABA reliever therapy	Maintenance oral corticosteroids
Able and willing to provide written informed consent	Oral sodium cromoglycate
Self-reported average use of a reliever inhaler on 2 episodes per week, over the 12 weeks prior to Visit 1	Inhaled long-acting muscarinic antagonists
F_{ENO} ⩾25 ppb at Visit 1	Self-reported use of ICS/LABA reliever therapy on ⩾8 episodes per week, over the 12 weeks prior to Visit 1
Ability to use the Turbuhaler device	Any use of systemic corticosteroids in the 6 weeks before Visit 1
Ability to perform F_{ENO} measurements at home on a regular basis	Previous intensive care unit admission for asthma ever
Registered with a general practitioner	Self-reported diagnosis of COPD, bronchiectasis, vocal cord dysfunction or interstitial lung disease
Willing to switch from current asthma treatment regimen	Current smokers (including e-cigarettes) and ex-smokers with a >20 pack-years smoking history, or asthma diagnosis after the age of 40 years in ex-smokers with ⩾10 pack-years history
	Any known or suspected contraindications to the study medications or their respective excipients
	History of any medical condition (including unstable cardiac disease) which may present a safety risk or impact the feasibility of the study, at investigator discretion
	Self-reported current pregnancy, breastfeeding or planned pregnancy at time of enrolment

SABA: short-acting β2-agonist; ICS: inhaled corticosteroid; LABA: long-acting β2-agonist; F_{ENO}: fractional exhaled nitric oxide; COPD: chronic obstructive pulmonary disease.

ICS with SABA reliever therapy, at baseline. They must have evidence of airway inflammation (F_{ENO} ⩾25 ppb) and report average reliever inhaler use on ⩾two occasions per week in the 12 weeks prior to enrolment.

Study interventions (item 11)

Participants will be randomised in equal proportion (1:1) to receive:

1. Intervention: budesonide/formoterol 200/6 µg dry powder inhaler (Symbicort Turbuhaler, AstraZeneca), one inhalation as needed for relief of asthma symptoms
2. Control: terbutaline 250 µg dry powder inhaler (Bricanyl Turbuhaler, AstraZeneca), two inhalations as needed for relief of asthma symptoms

In addition to the two randomised treatments, all participants will be allocated maintenance budesonide 200 µg dry powder inhaler (Pulmicort Turbuhaler, AstraZeneca). The dose of maintenance ICS allocated is determined *via* a standardised, automated algorithm as part of the enrolment process, based on their pre-study treatment regimen (supplementary table S2).

Study inhalers are dispensed at each visit and returned at all subsequent visits. Adherence and exposure to study medication will be determined by counting the number of doses remaining in used returned inhalers.

Participants will receive a written asthma action plan summarising their allocated study treatments. This includes written guidance on when to seek help due to worsening of asthma, based on the New Zealand asthma guideline action plans (supplementary figures S1 and S2) [13].

Participants will remain under the care of their usual general practitioner (GP) for the duration of the study, who will be informed of treatment allocation following randomisation. In the event of a deterioration in their asthma, participants are advised to seek medical assistance that may result in changes to their treatment for acute or chronic asthma management. If such an event occurs, participants are instructed to inform the study team at the earliest available opportunity where they may be invited to attend an unscheduled visit. Their deterioration of asthma will be assessed against the study definition of a moderate or severe asthma exacerbation, based on the American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus recommendations (supplementary table S3) [14]. If a participant experiences a

severe asthma exacerbation, has their treatment adjusted due to poor asthma control by their usual healthcare provider or reports poor asthma control (use of ⩾8 inhalations of terbutaline or ⩾4 inhalations of reliever budesonide–formoterol per day), an investigator (medical practitioner) may escalate the participant's maintenance treatment to ICS/LABA maintenance therapy, as per supplementary table S2, if judged as clinically appropriate. The escalation must ensure the daily maintenance ICS dose remains the same as at randomisation. If this requirement is judged as not clinically appropriate, they will be discontinued from the study treatment and/or withdrawn. A participant can only be escalated once in the study, and if further poor asthma control and/or a severe exacerbation is reported, they will be discontinued from study treatment and/or withdrawn. Other concomitant medication is permitted and will be recorded at each study visit.

Outcomes (item 12)

The primary outcome is F_{ENO} at 26 weeks, as measured at Visit 3.

Secondary outcome measures include the time-course of F_{ENO} at weeks 0–13 and 26, rate of asthma exacerbations and time to first severe asthma exacerbation at week 26, Asthma Control Questionnaire-5 (ACQ-5) at week 13 and 26, forced expiratory volume in 1 s (FEV_1) at week 13 and 26, and blood eosinophil count at week 26 (table 3).

Participant timeline (item 13)

There will be three clinic visits over 26 weeks for the purpose of trial enrolment, data collection, study completion and to help promote ongoing participant engagement with the study. Study procedures are illustrated in figure 1 and detailed in table 4.

Sample size (item 14)

The ATS recommends that a reduction in F_{ENO} of at least 20% after an intervention is clinically meaningful, or a reduction of >10 ppb for F_{ENO} measurements <50 ppb [10]. A 20% reduction can be expressed as a geometric mean ratio of F_{ENO} of 0.8. In MRINZ studies of similar asthma populations, the standard deviation (SD) of the change in the logarithm of F_{ENO} levels from baseline was about 0.6 [15, 16]. To detect a difference in the logarithmic F_{ENO} of 0.30 (equivalent to a geometric mean ratio of 0.74) with 90% power, 172 participants are needed. Allowing for a 5% dropout rate, this results in 90 participants per arm (180 in total). If the geometric mean F_{ENO} at baseline is 40 ppb, the target geometric mean F_{ENO} in the treatment group would be 30 ppb to detect this difference.

TABLE 3 Study outcomes and key end-points

End-points	Time point
Primary outcome: efficacy	
F_{ENO}	26 weeks
Secondary outcomes: efficacy	
F_{ENO} time course	0–12, 13 and 26 weeks
F_{ENO} variability	0–12, 13 and 26 weeks
Rate of severe, moderate, and moderate and severe asthma exacerbation	26 weeks
Number of ED or hospital admissions for asthma	26 weeks
Time to first severe asthma exacerbation	26 weeks
On-treatment FEV_1	13 and 26 weeks
ACQ-5	13 and 26 weeks
Peripheral blood eosinophil count	26 weeks
Secondary outcomes: safety	
Total composite corticosteroid dose (combined total inhaled and systemic dose for asthma)	26 weeks
Daily inhaled corticosteroid dose	26 weeks
Daily β_2-agonist actuations	26 weeks
Number of adverse events and severe adverse events	26 weeks
Proportion of participants who require treatment escalation due to severe exacerbation or poor asthma control	26 weeks
Proportion of participants who discontinue treatment or withdraw due to ⩾1 severe exacerbation or treatment failure	26 weeks

F_{ENO}: fractional exhaled nitric oxide; ED: emergency department; FEV_1: forced expiratory volume in 1 s; ACQ-5: Asthma Control Questionnaire 5.

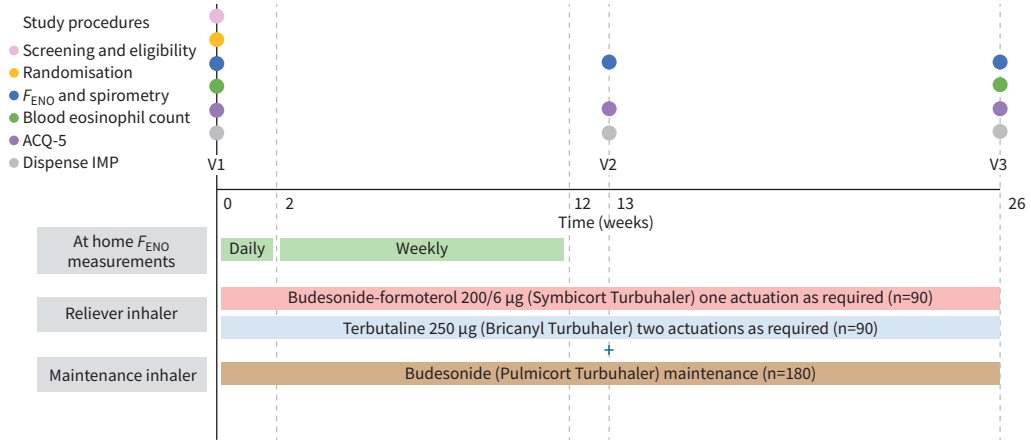

FIGURE 1 Study timeline. F_{ENO}: fractional exhaled nitric oxide; ACQ-5: Asthma Control Questionnaire 5; IMP: investigational medicinal product.

Recruitment (item 15)

MRINZ volunteer database, social media advertisements and referral from GPs will be used to achieve participant enrolment.

Assignment of interventions

Allocation (item 16)

Randomisation will be stratified according to each participant's baseline dose of ICS maintenance therapy (supplementary table S2) and if they report a severe asthma exacerbation in the previous 12 months. This will be performed using a computer-generated sequence created by the study statistician, independent of the investigators undertaking recruitment. The electronic case report form (eCRF) system will conceal the allocations and will release a participant's randomisation outcome at the time of randomisation. Study staff will not have access to the randomisation schedule.

Blinding (item 17)

This is an open-label study in which both study investigators and participants will be aware of the study treatment allocation.

Data collection, management and analysis

Data collection methods (item 18)

F_{ENO} will be measured at each planned study visit in accordance with ATS guidelines [17] using a Vivatmo *pro* device (Bosch, Waiblingen, Germany). To minimise inter-device variability on F_{ENO} [18], participants will perform follow-up F_{ENO} measurements on the same device throughout the study. On-treatment FEV_1 is measured at each planned study visit using an Easy-on-PC Spirometer (NDD Medical Technologies, Zurich, Switzerland) in accordance with ATS/ERS 2019 criteria [19] and results interpreted according to ATS criteria using Global Lung Function Initiative (GLI) reference ranges [20]. Reversibility testing is not required at any study visit. Asthma control will be assessed using the ACQ-5 at each study visit [21]. Peripheral blood eosinophil count will be measured at baseline and end of study (Awanui Laboratories, New Zealand).

At Visit 1, participants will be provided with a portable, handheld Vivatmo me device (Bosch, Waiblingen, Germany) in addition to a personalised calendar and all consumables required for 12 weeks of home F_{ENO} measurements. Participants are instructed to perform a daily measurement for the 14 days following randomisation, followed by a weekly measurement for the subsequent 10 weeks prior to attending Visit 2. Participants will be asked to perform the F_{ENO} measurement at the same time each day, but will not be given any specific instructions to withhold medication and/or avoid consuming specific foods/drinks prior to their home F_{ENO} measurements. They will receive text message reminders to improve adherence to their home F_{ENO} schedule. Home F_{ENO} results will be extracted from participant devices at the second study visit using the Vivatmo mobile app (Version 1.5.0, Bosch, Waiblingen, Germany). Participants will also complete a paper log of their home F_{ENO} measurements, which will be used if measurements cannot be extracted *via* the app.

TABLE 4 Schedule of study procedures

	Visit number			Unscheduled visit
	1	2	3	
Week	0	13	26	0–26
Day	0	91	182	0–182
Visit window, days	N/A	±7	±7	N/A
Confirm informed consent	X	X	X	X
Medical history and demographics	X			
Inclusion/exclusion criteria check	X			
Enrolment	X			
Randomisation	X			
Inhaler technique education and assessment	X	X	X	A/R
Medical review		X	X	A/R
1) Asthma exacerbations				
2) AEs				
3) SAEs				
4) Medication changes (including use of additional medication)				
Height and weight	X			
ACQ-5	X	X	X	
F_{ENO}[#]	X	X	X	
Dispensing home F_{ENO} device	X			
Review of home F_{ENO} measurements		X		
Spirometry	X	X	X	
Peripheral blood eosinophil count	X		X	
Dispense trial medication	X	X		A/R
Dispense/prescribe post-trial medication			X	A/R
Issue and explain asthma action plan	X	X	X	A/R
GP communications	X		X	A/R
Provide participant reimbursement	X	X	X	X

N/A: not applicable; A/R: as required; AEs: adverse events; SAEs: severe adverse events; ACQ-5: Asthma Control Questionnaire 5; F_{ENO}: fractional exhaled nitric oxide; GP: general practitioner. [#]: in addition to F_{ENO} measurements at study visits, participants also complete daily home F_{ENO} measurements for 2 weeks followed by weekly F_{ENO} measurements for 10 weeks between Visit 1 and 2.

Participants that discontinue study treatment, but do not withdraw their ongoing consent, will be invited to attend any remaining study visits to inform the intention-to-treat analysis population. Investigators will ensure that participants who complete the study, or discontinue the study treatment, have appropriate post-study treatment.

Data management (item 19)

Data will be collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the MRINZ [22, 23].

Statistical methods (item 20)

Statistical analysis will be by intention-to-treat by a statistician masked to treatment allocation. For the primary outcome, comparison of F_{ENO} at week 26 will be by ANCOVA, with baseline F_{ENO} as a covariate. The F_{ENO} data will be logarithm transformed and differences reported by both differences in logarithm F_{ENO} and the exponent of this, the latter of which is interpreted as the ratio of geometric means. For the primary outcome, we will also report the difference in outcome for Māori *versus* non-Māori, adjusted for treatment, and the difference between treatments, adjusted for ethnicity.

For the time course of F_{ENO} over 26 weeks, comparisons of treatments at each time point will be made by t-tests, as a simple comparison, and by mixed linear models, with the baseline value as a covariate, and each participant as a random effect, to account for repeated measurements. The proportion of participants in each treatment group with F_{ENO} <25, 25–50 or >5026 ppb will be displayed by Alluvial plots. The pattern of change with time will be explored with a time-by treatment interaction in a mixed linear model. For ACQ-5, blood eosinophil count and FEV_1 at 26 weeks, comparison will be by ANCOVA, with baseline as a covariate. Ordinal scale variables will be analysed by ordinal regression. The proportion of

participants in each treatment group with ACQ ⩽1.75, 7.5–1.5 and ⩾1.5 will be displayed by Alluvial plots. Comparison of the rate of severe, moderate and moderate & severe exacerbations per patient per year will be undertaken by Poisson regression with an offset for the time of observation and a fixed effect for the baseline GINA step treatment category and number of prior severe asthma exacerbations before recruitment. Over-dispersion will be evaluated prior to analysis and a corrected analysis applied as necessary. Survival analysis with Kaplan–Meier plots and Cox proportional hazards will be used to calculate the hazard ratio for time to first severe exacerbation.

SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) will be used.

Monitoring

Data and safety monitoring (item 21)

A Data Safety Monitoring Committee (DSMC) including clinicians with relevant respiratory and clinical trials expertise independent from the study has been formed. The DSMC will review all serious adverse events and protocol deviations/violations. No interim analysis is planned.

Harms (item 22)

All adverse events after enrolment and until final study visit will be recorded. The severity and relatability will be assessed by study doctors and reviewed by a Medical Monitor. Serious adverse events will be reported to the Sponsor on an expedited basis.

Auditing (item 23)

Regular monitoring of the study will also be undertaken by a sponsor-nominated Clinical Research Associate to ensure the study is conducted in compliance with the protocol, ethics approval and Good Clinical Practice guidelines.

Ethics and dissemination

Research ethics approval (item 24)

Ethics approval from the New Zealand North A Health and Disability Ethics Committee has been obtained (reference: 2022 FULL 13331).

Protocol amendments (item 25)

Substantive modifications to the study protocol will be submitted for prior approval to the ethics committee and communicated to relevant parties as necessary.

Consent (item 26)

Potential participants will be provided with an information sheet for a minimum of 24 h prior to the first study visit, and study doctors will obtain written informed consent from potential participants prior to any study procedure.

Confidentiality (item 27)

Participant identifiable data will be captured as part of source data, which will only be accessible to authorised site staff members. Participants will be allocated a unique participant number and identified only as this for the purpose of data analysis to maintain confidentiality.

Declaration of interests (item 28)

A conflict of interest statement is provided in the footnotes.

Access to study data (item 29)

Only the sponsor will have access to the final trial dataset.

Ancillary and post-trial care (item 30)

All participants are prescribed appropriate post-study inhalers based on national guidelines. Participants that experience harm because of this study are entitled to government sponsored no-fault personal injury insurance in New Zealand (Accident Compensation Corporation).

Dissemination policy (item 31)

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. A lay summary of the results will be provided to study participants.

Informed consent materials (item 32)

An example of the study consent form is provided in the supplementary material.

Discussion

There are several reasons why maintenance ICS plus separate reliever inhaler use will continue. Firstly, ICS is more widely available and costs less than combination ICS/LABA, especially important for low- and middle-income countries [24], and so providing evidence for a regimen that could reduce the total number of ICS/LABA inhalers required is important. ICS without combination LABA inhaler is reported to be used by between 12.6% and 51.9% of patients with asthma worldwide, representing the second most frequently used inhaled medicine for asthma behind SABAs [8]. Secondly, patients may have reactions to specific inhaled medication and/or their excipients, so the need for a range of medication and medication classes will continue. Finally, patient preference is vital to achieve optimal personalised care, and some patients may prefer a separate maintenance and reliever inhaler combination. As maintenance ICS use will continue, it is essential to provide evidence for the optimum reliever inhaler to accompany this therapy. If ICS/formoterol reliever is more effective than SABA reliever when taken with maintenance ICS therapy, as has been shown both with and without ICS/formoterol maintenance [5–7], then it could contribute to a reduction in the morbidity associated with asthma.

An important strength of this study is the inclusion of participants at different doses of ICS at baseline, which results in different doses being allocated as maintenance treatment in the study. This will examine if there is different efficacy in reliever therapy across a range of daily maintenance ICS doses and increase the generalisability of the study to real-world ICS use.

F_{ENO} was chosen as the primary outcome for this study as it is a reproducible, noninvasive, validated marker of T2 inflammation [10] making it the prime candidate to investigate the anti-inflammatory action of ICS/formoterol [9]. It is also clinically relevant, as patients with raised F_{ENO} may be up to four times more likely to have a severe exacerbation [25], and treatment algorithms that include F_{ENO} as part of an asthma assessment reduce the risk of an exacerbation by around 30% [26]. Whilst studies of ICS/formoterol-based regimens have been superior to SABA-based regimens irrespective of T2 biomarkers [27, 28], a *post hoc* analysis of a moderate–severe asthma RCT reported the greatest reduction in severe exacerbations in patients with raised serum eosinophils, another T2 biomarker [28]. Investigating the response of specific T2 biomarkers to different reliever therapy regimens will result in a better appreciation of the mechanism(s) of action for ICS/formoterol reliever therapy. To date, four RCTs have reported the effect on F_{ENO} with ICS/formoterol reliever [15, 16, 29, 30], either when taken as reliever therapy only [15, 16] or together with maintenance ICS/formoterol [29, 30]. Whilst these studies have reported reductions in F_{ENO} with ICS/formoterol reliever therapy, interpretation is limited by infrequent measurements and different comparator maintenance therapy [15, 16, 29, 30], and also by the small number of participants in short duration studies [29, 30]. Furthermore, the speed of onset for the anti-inflammatory action of maintenance ICS is understood [31] but has not been described for ICS/formoterol reliever therapy.

The study will also report on other important clinical outcomes in asthma, as per ATS/ERS consensus recommendations [14]. These include moderate and severe asthma exacerbations, the effect on FEV_1 and symptom control as assessed by the ACQ-5. Composite corticosteroid exposure, which includes both ICS and systemic corticosteroid exposure for asthma, in addition to ICS exposure, will be reported.

It is not possible to conduct a blinded trial for several reasons. Firstly, commercially available Turbuhalers can be readily identified by different colour bases. Secondly, participants that are randomised to different arms are given different instructions for the number of reliever inhaler inhalations per use: the control arm is instructed to take two inhalations of terbutaline 250 µg and the treatment arm is instructed to take one inhalation of budesonide/formoterol 200/6 µg. Furthermore, it is not possible to blind participants to their respective at-home F_{ENO} readings, as the Vivatmo me devices display the F_{ENO} value immediately following a measurement. This step is required for participants to know that their measurement has been completed successfully, and for data-security purposes (*e.g.* in the event their home device malfunctions or is lost) they are asked to also record this value in a paper log.

In conclusion, this RCT will be the first to examine the anti-inflammatory effect, efficacy and safety of ICS/formoterol reliever therapy *versus* SABA reliever therapy in adult patients with asthma who take maintenance ICS, providing vital evidence for a fundamental gap in the evidence for ICS/formoterol reliever therapy. It will also provide a novel insight into the onset, time-course and magnitude of changes in F_{ENO} with ICS/formoterol reliever therapy.

Provenance: Submitted article, peer reviewed.

The INFORM ASTHMA Trial study team: Augustus Anderson, Christina Elder, Trisha Falleni, Kyley Kerse, Joseph Kulathinal, Francesca Lynch, Tony Mallon, John Martindale, Ruth Semprini, Nick Shortt, Jenny Sparks and Michaela Walton.

Ethics statement: Ethics approval has been granted from the North A Health and Disability Ethics Committee, New Zealand (Reference 2022 FULL 13331) and will be conducted in compliance with this ethics approval and Good Clinical Practice guidelines.

This clinical trial is prospectively registered with Australian New Zealand Clinical Trials Registry as ACTRN12622001304729.

Conflict of interest: J. Noble, O. Bean, P. Bruce, M. Black, R. Sayers, R. Cullen, B. Black, M. Holliday, L. Kirton, B. Perry, A. Eathorne and M. Weatherall have no conflicts of interests to declare. I. Pavord has received consulting fees from GSK, Sanofi/Regeneron, AstraZeneca and Circassia; support for attending meetings and/or travel from GSK, Sanofi/Regeneron and AstraZeneca; and has stock or stock options in Upstream Bio and Mybiometry. R. Beasley has received institutional research funding from AstraZeneca and Teva, and personal fees from AstraZeneca, Avillion, Teva Pharmaceuticals and Cipla outside the submitted work; and is Chair of the Asthma Foundation of New Zealand Adolescent and Adult Asthma Guidelines Group, and was a member of the Board of Directors of the Global Initiative for Chronic Obstructive Lung Disease.

Support statement: This study was supported by AstraZeneca grant ESR-23-22270. Funding information for this article has been deposited with the Open Funder Registry.

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