Randomised controlled trial of a new relief inhaler in mild asthma: the RELIEF trial (RELIEF)

Statistical Analysis Plan

Final version 1.0
(01 Oct 2025)

Based on Protocol version 4.0 (dated 10 Apr 2025)

Trial registration: ISRCTN29579666

Approval

The following people have reviewed the Statistical Analysis Plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas.

Name	Job title	Trial Role	Signature	Date
Yuanfei Su	Medical Statistician	Trial Statistician (Author)		Oct 2, 2025
Lucy Bradshaw	Senior Medical Statistician	Senior Trial Statistician	Lucy Bradshaw	2-Oct-2025
Matthew Martin	Clinical Associate Professor	Chief Investigator	M.J.Martin M.J.Martin (Oct 3, 2025 09:52:43 GMT+1)	Oct 3, 2025

List of contributors and reviewers

Name	Job title	Affiliation	Role on the trial	SAP Contribution
Yuanfei Su	Medical Statistician	Nottingham Clinical Trials Unit	Trial Statistician	Author
Toyin Bello	Medical Statistician	Nottingham Clinical Trials Unit	Trial Statistician	Reviewer
Lucy Bradshaw	Senior Medical Statistician	Nottingham Clinical Trials Unit	Senior Trial Statistician	Reviewer
Matthew Martin	Clinical Associate Professor	Respiratory Medicine	Chief Investigator	Reviewer
Alan Montgomery	Director Nottingham Clinical Trials Unit	Nottingham Clinical Trials Unit	Co-investigator	Reviewer
Hugh Jarrett	Senior Trial Manager	Nottingham Clinical Trials Unit	Senior Trial Manager	Reviewer
Martyn Lewis	Reader in Medical Statistics	Primary Care Centre Versus Arthritis, School of Medicine, Keele University	DMC Statistician	Reviewer
Abin Thomas	Research Associate - Statistics	Cardiff University, Centre for Trials Research	TSC Statistician	Reviewer

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Abbreviations

Abbreviation	Description
DMC	Data monitoring committee
SAP	Statistical Analysis Plan
TMG	Trial Management Group
TSC	Trial Steering Committee
ACQ5	Asthma Control Questionnaire

Changes from protocol

The table below details changes to the planned analyses in the SAP compared to the protocol, which after discussion with the TMG, are not considered to require a protocol amendment.

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification
Secondary endpoints	ACQ5 symptom questionnaire at 12 months post-randomisation	Section 2.5	ACQ5 at final follow-up	Due to early closure of the trial, majority of the randomised participants will not be followed up at 12 months post randomisation. Data will be collected at the final follow-up point for each participant either during follow-up assessment or

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification
				via online survey. The data collection duration will depend on the completion method of ACQ5. Full details can be found in Section 3.6 – Follow up duration for ACQ5.
Secondary endpoints	Number of severe asthma exacerbations over a 12-month period post-randomisation	Section 2.5	Number of severe asthma exacerbations over participant's follow-up period	Due to early closure of the trial, majority of the randomised participants will not be followed up at 12 months post randomisation. The data collection duration will depend on participant's trials status at the end of March 2025. Full details can be found in Section 3.6 – Follow up duration.
Secondary endpoints	- Number of hospital admissions for asthma in 12-month period post-randomisation - Number of emergency department attendances for asthma in the 12 months post-randomisation - Total SABA, ICS and ICS/formoterol inhalers prescribed	Section 2.5	- Number of hospital admissions for asthma over participant's follow-up period - Number of emergency department attendances for asthma over participant's follow-up period - Total SABA, ICS and ICS/formoterol inhalers	Due to early closure of the trial, majority of the randomised participants will not be followed up at 12 months post randomisation. Data collection duration will be: • 12 months post-randomisation for participants randomised before April 2024

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification
	in the 12 months post - randomisation		prescribed over participant's follow-up period	• date of randomisation to the scheduled follow-up date in March 2025 otherwise

Amendments to versions

Protocol Version	Updated SAP Version	Date	Change/comment	Statistician	Timing in relation to unblinded interim monitoring/analysis	Timing in relation to unblinding of Trial Statistician

1 INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the RELIEF trial sponsored by NIHR. The results reported will follow the strategy set out here, which adheres to the guidelines for the content of a statistical analysis plan (Gamble et al, 2017).

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is appropriate.

2. Explain in detail how the data will be handled and analysed to enable others to perform or replicate these analyses

Additional exploratory or auxiliary analyses of data not specified in the protocol may be included in this analysis plan.

This analysis plan will be published on the study website, hence will be available publicly. It will be uploaded with the main papers, if required, when they are submitted for publication. Additional analyses suggested by reviewers or editors will be performed if considered appropriate. This should be documented in a file note.

Any amendments to the statistical analysis plan (SAP) after the first version of the SAP is agreed and signed off will be made by the blinded statisticians and will be described and justified.

Health economic and qualitative analysis plans are beyond the scope of this document.

2 STUDY SYNOPSIS

2.1 Study background and rationale

Table 1: Synopsis of planned study design and procedures[1]

Title	Randomised controlled trial of a new relief inhaler in mild asthma: the RELIEF trial
Acronym	RELIEF
Short title	A new relief inhaler for mild Asthma
Chief Investigator	Dr Matthew Martin
Objectives	The overall aim is to determine the clinical effectiveness, cost effectiveness and acceptability, of replacing short-acting beta agonists (SABA) inhalers, containing Salbutamol, with inhalers containing ICS/formoterol in patients with asthma treated with low dose inhaled corticosteroid (ICS) maintenance treatment. **Primary Objective:** • To compare the time to first severe asthma exacerbation (defined as treated with 3 or more days of systemic corticosteroids) in patients using regular low dose ICS and randomised to either SABA (Salbutamol) or ICS/formoterol for symptom relief. **Secondary Objectives** • To compare the overall ICS dose used in both groups as a marker of safety. • To compare the number of severe asthma exacerbations including number of hospital attendances. • To compare the cost effectiveness of these two strategies. • To explore the health care professional and patients' views of replacing the Salbutamol inhaler. • Health-related quality of life: EQ-5D-5L at baseline, 3, 6 9 and 12 months.
Trial Configuration	A multicentre, 1:1 randomised, open-label, standard care-controlled trial that will include 2300 individuals with a clinical diagnosis of mild asthma, treated with low dose ICS with Salbutamol as required.
Setting	Primary care
Sample size estimate	A sample size of 1,104 participants per group is required to detect a hazard ratio of 0.65 (assuming at least 13% of the participants randomised to low dose ICS plus Salbutamol have a severe exacerbation over the 12-month follow-up period) with 90% power and two-sided 5% significance level. Based on 97% of randomised participants being included in the analysis of time to severe exacerbation, a total sample size of 2,300 participants is required.
Number of participants	2300
Eligibility criteria	**Inclusion criteria:** 1. Patients aged 18 and over with a clinical diagnosis of mild asthma*

	2. Treated with low dose ICS** 3. Prescribed 11 or fewer canisters of Salbutamol in the last 12 months*** 4. Ability to provide written/electronic informed consent. *For the purposes of this trial "mild asthma" is defined as those patients with an existing clinical diagnosis of asthma (recorded in medical records) and treated with either Salbutamol alone or low dose ICS and Salbutamol. No further diagnostic tests will be undertaken to confirm asthma or its severity as we want the trial to be pragmatic in nature and, therefore, include patients who are currently treated for mild asthma. **low dose ICS is defined as up to and including 400 mcg BDP/day or equivalent ***Patients using Salbutamol alone and using 3 or more inhalations per week can be included if started on low dose ICS as part of their routine care for a minimum of 1 month before trial commencement. **Exclusion criteria:** 1. Salbutamol used only to prevent exercise induced asthma. 2. Other respiratory or non-respiratory diagnosis which will affect the trial interpretation in the view of the investigator (this includes, but is not limited to, smoking related Chronic Obstructive Pulmonary Disease (COPD) and clinically significant bronchiectasis). 3. Pregnancy or intention to become pregnant.
Description of interventions	**Intervention arm:** daily low dose ICS & ICS/Formoterol as required for symptom relief. **Usual Care arm:** daily low dose ICS & and inhaled Salbutamol for symptom relief.
Duration of trial	The trial will last for 44 months overall and will employ a rapid recruitment process of approximately 2-3 months at each primary care site. Randomised participants will spend 12 months in the trial.
Randomisation and blinding	All participants consenting to the trial will be randomised 1:1, using a minimisation algorithm with a random element, to as required combination ICS/formoterol or as required Salbutamol for symptom relief. The minimisation variables will be: • GP practice • Asthma exacerbation requiring at least 3 days of systemic steroids in the last 12 months • Treatment with low dose ICS started more than 1 month but less than 3 months ago versus ICS treatment started 3 or more months ago. This is an unblinded trial, so no emergency unblinding processes are necessary.
Outcome measures	**Primary outcome** • The primary outcome is time to first severe asthma exacerbation, defined as treatment with systemic corticosteroids for an asthma worsening, for at least 3 days. **Secondary outcomes** • Number of severe asthma exacerbations

	• Number of hospital admissions for asthma • Number of emergency department attendances for asthma • Total SABA, ICS and ICS/formoterol inhalers prescribed • ACQ5 at 12 months • Acceptability of new treatment will be assessed via an embedded qualitative study

1 – Note recruitment to the trial was closed in January 2025 prior to reaching the planned sample size at the request of the funder. Final follow-ups assessments will be conducted between March and July 2025

2.2 Sample size and justification

The trial has been powered to detect a hazard ratio of 0.65 in the time to first severe asthma exacerbation assuming that 13% of participants in the group allocated to low dose ICS plus Salbutamol have a severe exacerbation over the 12-month follow-up period. A sample size of 1,104 participants per group is required to detect a hazard ratio of 0.65 (i.e. reduction to 8.7% having a severe exacerbation in the low dose ICS plus ICS/formoterol as required group) with 90% power and two-sided 5% significance level. Based on 97% of randomised participants being included in the analysis of time to severe exacerbation (as in the FAST HTA trial(1)), a total sample size of 2,300 participants is required.

The assumption that 13% of participants in the group allocated to low dose ICS and Salbutamol group will have a severe asthma exacerbation over the one-year follow-up period is taken from the recent PRACTICAL open label randomised controlled trial comparing ICS/formoterol reliever as required to low dose ICS and SABA in New Zealand (2). The eligibility criteria for the PRACTICAL trial were very similar to our proposed trial. The PRACTICAL trial recruited patients with a self-reported doctor diagnosis of asthma either using SABA as a reliever alone or low/moderate dose ICS and SABA prior to enrolment. Over the 52-week follow-up, 59 of the 448 participants (13%) allocated to low dose ICS and SABA experienced an asthma exacerbation requiring the use of 3 or more days of oral corticosteroids.

However, if the percentage of participants experiencing a severe exacerbation is lower than expected, there is greater than 80% power to detect a hazard ratio of 0.65 if at least 10% of participants in the low dose ICS and SABA group have a severe exacerbation.

It is believed that a target hazard ratio of 0.65 is (a) plausible based on previous trials of ICS/formoterol as required versus low dose ICS and SABA and (b) sufficiently clinically important to change practice. In more severe asthma, a relative risk of severe exacerbations of 0.66 (95% CI 0.6 to 0.72) was observed for ICS/formoterol compared to SABA as reliever therapy in patients using ICS/formoterol for maintenance in a review to inform the NICE guidelines in 2017 (3). Hazard ratios for time to severe asthma exacerbation in the four previous RCTs of ICS/formoterol as required compared to low dose ICS + SABA as required in patients with mild asthma ranged from 0.41 to 0.96 (2, 4-6). In theory the combination of maintenance ICS for daily control plus ICS/formoterol as required is likely to lead to better asthma control than ICS/formoterol as required with no maintenance ICS.

2.3 Randomisation

Participants consenting to the trial will be randomised 1:1, using a minimisation algorithm with a random element, to as required combination ICS/formoterol or as required Salbutamol for symptom relief. The minimisation variables will be:

- GP practice
- Asthma exacerbation requiring at least 3 days of systemic steroids in the last 12 months
- Treatment with low dose ICS started more than 1 month but less than 3 months ago versus ICS treatment started 3 or more months ago.

Concealed allocation will be via a secure, web-based randomisation service created and maintained by NCTU. Randomisation can be performed by suitably trained GP practice staff assigned this task on the Delegation of Responsibilities Log, following confirmation of eligibility by a GP.

All medication will be obtained from normal high street pharmacy supplies and used in accordance with the allocation and prescription.

2.4 Blinding and breaking of blind

Blinding of participants and health professionals is not possible in this trial. Theoretically, knowledge of group allocation could influence participant inhaler use and clinical decisions around treatment.

The trial statisticians and TSC members will be blinded to participant group allocations. An unblinded independent NCTU statistician will produce closed reports for the DMC. This is an unblinded trial, so no emergency unblinding processes are necessary.

2.5 Outcome measures

Table 2: Summary of the outcome measures

Outcome measure	Description	Source	Type	Method of aggregation	Method of analysis
Primary outcome					
Time to first severe exacerbation (defined as treated with 3 or more days of systemic corticosteroids)	Time from randomisation to date first started to take systemic corticosteroids for 3 or more days for asthma exacerbation up to final follow-up point for each participant. Follow-up duration depends on participant's trials status at the end of March 2025. Full details can be found in Section 3.6 – Follow up duration.	Measured by routine automated text/email follow-up or patient's prescribed medication record	Time to event	Number and percentage, as well as incidence rate in each group with a severe exacerbation Time to severe exacerbation presented in Kaplan Meier curves	As described in protocol for the primary outcome, using Cox regression model, adjusting for minimisation factors
Secondary outcome					
Number of severe asthma exacerbations over participant's follow-up period	Severe exacerbations defined as treated with 3 or more days of systemic corticosteroids. Start date of each asthma exacerbation should be 7 days or more after the end date of previous exacerbation to classify the exacerbations as separate events. Follow-up duration depends on participant's trials status at the end of March 2025. Full details can be found in Section 3.6 – Follow up duration.	Measured by routine automated text/email follow-up or patient's prescribed medication record	Count	Means and standard deviations, as well as incidence rate in each group Frequencies and percentages with 0, 1, and ≥ 2 severe exacerbations	Using mixed-effect negative binomial model adjusting for minimisation factors and incorporating exposure time (follow-up duration)

Outcome measure	Description	Source	Type	Method of aggregation	Method of analysis
Number of hospital admissions for asthma over participant's follow-up period	Hospital admission defined as overnight stay in hospital due to asthma. Data collection duration will be: • 12 months post-randomisation for participants randomised before April 2024 • date of randomisation to the scheduled follow-up date in March 2025 otherwise	Review of GP medical records at the end of the trial	Count	Number and percentages with 0, 1 and ≥ 2 hospital admissions for asthma	Descriptive only
Number of emergency department attendances for asthma over participant's follow-up period	Emergency department defined as hospital A&E attendance due to asthma. Data collection duration will be: • 12 months post-randomisation for participants randomised before April 2024 • date of randomisation to the scheduled follow-up date in March 2025 otherwise	Review of GP medical records at the end of the trial	Count	Number and percentages with 0, 1 and ≥ 2 emergency department attendances for asthma	Descriptive only
Total ICS/formoterol inhalers prescribed over participant's follow-up period	Data will be obtained using medical record at the end of the trial. Data collection duration will be: • 12 months post-randomisation for participants randomised before April 2024 • date of randomisation to the scheduled follow-up date in March 2025 otherwise	Review of GP medical records at the end of the trial	Count	Means and standard deviations, as well as incidence rate in each group	Descriptive only

Outcome measure	Description	Source	Type	Method of aggregation	Method of analysis
Total SABA inhalers prescribed over participant's follow-up period	Data will be obtained using medical record at the end of the trial Data collection duration will be: • 12 months post-randomisation for participants randomised before April 2024 • date of randomisation to the scheduled follow-up date in March 2025 otherwise	Review of GP medical records at the end of the trial	Count	Means and standard deviations, as well as incidence rate in each group	Descriptive only
Total ICS inhalers prescribed in over participant's follow-up period	Data will be obtained using medical record at the end of the trial Data collection duration will be: • 12 months post-randomisation for participants randomised before April 2024 • date of randomisation to the scheduled follow-up date in March 2025 otherwise	Review of GP medical records at the end of the trial	Count	Means and standard deviations, as well as incidence rate in each group	Using mixed-effect negative binomial model adjusting for minimisation factors and incorporating exposure duration (follow-up duration for inhaler prescription and hospital visits)
ACQ5 at final follow-up	ACQ5 questionnaire is applied to determine the adequacy of asthma control. ACQ5 consists of 5 questions with responses on a 7-point scale (0 = no impairment, 6 = maximum impairment). Five items are equally weighted and ACQ5 score is the mean of the five items. Data will be collected at the final follow-up point for each participant either during	Measured by ACQ5 questionnaire	Continuous	Means and standard deviations in each group	Using mixed-effect linear regression model adjusting for minimisation factors, baseline ACQ5, and follow-up duration for ACQ5.

Outcome measure	Description	Source	Type	Method of aggregation	Method of analysis
	follow-up assessment or via online survey. The data collection period will depend on the completion method of ACQ5. Full details can be found in Section 3.6 – Follow up duration for ACQ5.				
Health related quality of life: EQ-5D-5L	EQ-5D-5L will be analysed by health economist				

2.6 Trial committees

A Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) will be assembled to oversee the trial. The general purpose, responsibilities and structure of the committees are described in the protocol. Further details of the roles and responsibilities of the TSC and DMC can be found in their charters agreed prior to the start of recruitment to the trial.

3 GENERAL ANALYSIS CONSIDERATIONS

3.1 Primary estimand

Attribute	
Target population	Patients with asthma treated with low dose inhaled corticosteroid (ICS) maintenance treatment
Endpoint	Severe asthma exacerbation - defined as treated with 3 or more days of systemic corticosteroids
Treatment conditions	**Intervention Group -** daily low dose ICS & ICS/Formoterol as required for symptom relief **Usual Care Group -** daily low dose ICS & inhaled SABA (salbutamol) for symptom relief.
Population level summary measure	Hazard ratio
Intercurrent events	
Treatment discontinuation	Treatment policy strategy
Non-adherence to the intervention	Treatment policy strategy
Consent withdrawal	While at risk
Death	While at risk

3.2 Analysis sets

Outcome	**Analysis set**	**Definition**
Primary outcome/ Secondary outcome – Number of severe asthma exacerbations over participant's follow-up period	Primary	All randomised participants who are followed up for at least a month by the end of the trial and who do not have a severe asthma exacerbation on the day of randomisation will be analysed according to randomised group (as randomised) regardless of adherence with the allocated intervention.
Other secondary outcomes	Secondary	All randomised participants will be analysed according to randomised group (as randomised) regardless of adherence with the allocated intervention.

Outcome	Analysis set	Definition
Safety outcomes	Secondary	All randomised participants will be analysed according to randomised group (as randomised) regardless of adherence with the allocated intervention.

3.3 Interim analysis

No planned interim analysis

3.4 Timing of final analysis

The final analysis will be conducted after database lock and release of the treatment allocations.

3.5 Statistical software

All analysis will be performed using Stata v18 or above.

3.6 Derived variables

Outcome derivations are referred to Table 1.

Variable	Derivation
Strength of ICS inhaler prescribed (mcg BDP/day)	To calculate the BDP-equivalent ICS dose per puff, different multiplier factors will be applied depending on the type of ICS inhaler: • A dose multiplier of 2 will be used for fluticasone propionate and fine-particle beclometasone. • A dose multiplier of 1.25 will be used for ciclesonide. The strength of the prescribed ICS inhaler is calculated by multiplying the BDP-equivalent ICS dose per puff by the number of puffs per day.
Pack years (cigarettes)	Number of packs of cigarettes smoked per day multiplied by the number of years smoked.
Follow-up duration (months)	Follow-up duration is derived as follows: - Participants who reached 12 months before April 2025 and completed final follow assessment: date of 12 months post randomisation minus date of randomisation - Participants who did not reach 12 months post-randomisation by the end of March 2025 and who completed the final follow-up assessment or had a medical record check: the date of the medical record check or the date of the final follow-up assessment (whichever is later) minus the date of randomisation. - Participants who died/withdrew/did not complete final follow-up assessment without medical record checked: latest date of final text message response/death/withdrawal minus date of randomisation.

	- Participants who died/withdrew/did not complete final follow-up assessment with medical record checked: date of medical record check minus date of randomisation If the derived follow-up duration is more than 12 months for participants who did not reach 12 months post-randomisation by the end of March 2025, the follow-up duration will be truncated at 12 months.
Follow-up duration for inhaler prescription and hospital visit (months)	Follow-up duration for inhaler prescription and hospital visit is derived as follows: - 12 months post-randomisation for participants randomised before April 2024 - Date of randomisation to the scheduled follow-up date in March 2025 minus date of randomisation otherwise Derived follow-up duration for inhaler prescription and hospital visit will be rounded to the nearest month.
Follow-up duration for ACQ5 (months)	Follow-up duration for ACQ5 is derived as follows: - Participant who completed ACQ5 online: date of completion minus date of randomisation - Participant who completed ACQ5 during final follow-up assessment: date of final follow-up assessment minus date of randomisation. Follow-up duration will be 12 months if participants reached 12 months post-randomisation before April 2025. Derived follow-up duration for ACQ5 will be rounded to the nearest month.

3.7 Procedures for missing data

3.7.1 Missing outcome data

Missing data for the primary outcome are expected to be minimal. Medical records will be checked for all participants at the end of the 12-month follow-up or at the end of the trial data collection, whichever occurs first. For participants who withdrew consent or died prior to the end of the trial, medical records will be checked to if confirmed if any severe asthma exacerbation occurred while they were in the trial.

Secondary analysis will be based on the observed data, and no imputation will be performed for missing data.

3.7.2 Missing baseline data

Missing data for baseline characteristics will be summarised descriptively as part of the baseline data.

3.7.3 Missing items in ACQ5 questionnaire

ACQ5 is completed by participants through an online survey. The score for ACQ5 can only be calculated if all five items are fully answered. ACQ5 score will therefore be missing for participants who do not complete all five items.

4 DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1 Participant flow

The flow of participants through the trial will be summarised in a CONSORT diagram that will include the number of patients invited, number of patients consented, number of participants randomised to two groups, number of participants with primary outcome available, and the reason for primary outcome not available.

4.2 Baseline characteristics

Participants will be described by treatment group with respect to baseline demographic and clinical characteristics (including randomisation minimisation variables):

- Biological sex
- Age (years)
- Ethnicity
- Age at asthma diagnosis (years)
- Deprivation status (Decile of Index of multiple deprivation)
- Smoking status
- Current use of vape
- Asthma exacerbation requiring at least 3 days of systemic steroids in the last 12 months
- Ever had asthma exacerbation requiring at least 3 days of systemic steroids
- Time since GP prescribed low dose ICS treatment
- Type of ICS inhaler used
- Strength of ICS inhaler prescribed (mcg BDP/day)
- Inhaled steroid only used at certain times of the year
- Other medical conditions (eczema, hay fever, nasal polyps) ever diagnosed
- ACQ5 score at baseline

Continuous data will be summarised in terms of the mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations. Categorical data will be summarised in terms of frequency counts and percentages. No formal statistical comparisons will be made.

5 ASSESSMENT OF STUDY QUALITY

5.1 Integrity of Randomisation Method

Participants were randomised into either group of daily ICS and as required SABA inhaler or daily ICS and as required combined inhaler on a 1:1 ratio, using minimisation based on the following factors:

- GP practice
- Asthma exacerbation requiring at least 3 days of systemic steroids in the last 12 months

- Treatment with low dose ICS started more than 1 month but less than 3 months ago versus ICS treatment started 3 or more months ago.

The number of participants who were randomised in error and subsequently withdrawn from the trial will be summarised by allocated group. For those withdrawn on the day of randomisation, data regarding the primary outcome will not be used for analysis. For those withdrawn after the day of randomisation, medical records will be checked to obtain data on asthma exacerbation for use in the primary outcome analysis.

5.2 Adherence

As the trial intervention is as required for asthma symptom relief, it will not be possible to directly monitor treatment adherence. Total number of SABA inhalers prescribed is a secondary outcome to compare SABA usage in the two groups.

5.3 Follow-up and discontinuations

5.3.1 Month 1 post randomisation follow-up

Participants will be followed up by staff at the GP practice. The number and percentage of participants with follow-up completed will be presented. The number of days to complete follow-up from the date of randomisation will be summarised using the mean, median, lower and upper quartiles, minimum, and maximum.

5.3.2 Month 2 to 11 post randomisation follow-up

Participants will be followed up monthly via text message, asking whether they have experienced any asthma exacerbation in the past four weeks during months 2 to 11 post-randomisation. If a participant reports an asthma exacerbation, a follow-up phone call from GP staff will be made to confirm the date and duration of the reported exacerbation. Due to the early closure of the trial, the final text messages were sent to all participants in Feb 2025.

Due to the early closure of the trial, the follow-up duration will vary for participants depending on when they entered the trial. The number of participants expected to be followed up will be presented according to follow-up timepoints. The number of participants followed up, the number not followed up, and the reasons for non-follow-up will be displayed for each timepoint and allocated group.

5.3.3 End of trial follow-up

Due to early closure of the trial, participants randomised before April 2024 will be invited to attend the final follow-up assessment between March and September 2025. The number of participants completing the final follow up assessment, the reasons for non-completion of follow-up, and the duration of follow-up in the trial will be summarised for each allocated group.

5.4 Protocol deviations

The number of participants with at least one protocol deviation and number of each type of protocol deviations will be presented. Protocol violations will be summarised and presented as described for protocol deviations. All protocol deviations/violation will be listed along with date of reported, days from randomisation to protocol deviation/violation, and details of protocol deviation/violation.

6 ANALYSIS OF EFFECTIVENESS

6.1 Primary analysis

The main approach to between group comparisons will be based on intention-to-treat, analysing participants in the groups to which they were randomised regardless of adherence with the allocated intervention.

The primary outcome, time to severe asthma exacerbation treated with 3 or more days of systemic corticosteroids, will be analysed using a Cox proportional hazards regression model adjusted for minimisation variables with GP practice a random effect. A hazard ratio and 95% confidence interval will be estimated for the between group comparison. Kaplan Meier curves will be presented for time to first severe asthma exacerbation by allocated group.

The number and frequency of participants who reported severe asthma exacerbations during their follow-up period will be presented. Additionally, the total person-years of follow-up will be reported for each group.

For participants who do not have a severe asthma exacerbation, time to first severe asthma exacerbation will be censored. Dates used for censoring are as follows:

Category	Censored at
Reached 12 months before April 2025 and completed final follow assessment	Date of 12 months post randomisation
Did not reach 12 months post-randomisation by the end of March 2025 and completed the final follow-up assessment or had a medical record check	Date of the medical record check or the date of the final follow-up assessment (whichever is later). Truncated at 12 months post randomisation date if latest of final follow-up assessment/medical record check more than 12 months post randomisation.
Died/withdrew/did not complete final follow-up assessment without medical record checked	Latest date of final text message response/death/withdrawal
Died/withdrew/did not complete final follow-up assessment with medical record checked	Date of medical record check

Proportional hazard will be checked using a log-log plot for randomised groups, whether participant experienced asthma exacerbation requiring at least 3 days of systemic steroids in the last 12 months, and whether participant was treated with low dose ICS started more than 1 month but less than 3 months ago. If non-proportional hazards are detected, the covariate will be included in the model as a time-dependent covariate.

In the event of non-convergence of the model specified above, a fixed-effect Cox proportional hazard model adjusting for all other minimisation factor except GP practice will be used.

6.2 Sensitivity analysis of primary outcome

We expect primary outcome data to be able to be collected for nearly all randomised participants.

However, time to first severe asthma exacerbation will be censored prior to the participants expected end of trial follow-up date if participants withdraw consent. Withdrawn participants will be censored at different dates after date of withdrawal in the sensitivity analysis to investigate the potential impact of these participants on the between group estimate.

6.3 Supplementary analysis of primary outcome

No supplementary analysis is planned.

6.4 Subgroup analysis of primary outcome

Subgroup analyses for the primary outcome will be implemented for the following:

- Smoking status
- Whether the participant ever had an asthma exacerbation, that required 3 or more days of oral steroids

Analysis will be performed by including appropriate interaction terms in the analysis model for the primary outcome to explore the difference in treatment effect across subgroups.

The trial is not powered to detect any interactions hence the subgroup analyses will be treated as exploratory.

6.5 Secondary outcomes

Count outcomes

The following secondary outcomes

- Number of severe asthma exacerbations over participant's follow-up period
- Total ICS inhalers prescribed over participant's follow-up period

will be analysed using mixed-effect negative binomial regression, adjusting for minimisation factors with GP practice as a random effect. As participants will be followed up for different durations due to the early closure of the trial, months of follow-up will be incorporated in the model. The between-group difference will be reported using the adjusted rate ratio along with a 95% confidence interval.

The number of events will be summarised in each allocated group using mean, median, lower & upper quartiles, minimum, maximum and number of observations. Additionally, events will be categorised with number and percentage presented for the number of severe asthma exacerbations over participant's follow-up period.

Total person-years and incidence rate will also be reported for both outcomes.

Number of inhalers prescribed

- Total ICS/formoterol inhalers prescribed over participant's follow-up period
- Total SABA inhalers prescribed over participant's follow-up period

will be summarised descriptively with number of inhalers summarised using mean, median, lower & upper quartiles, minimum, maximum and number of observations in each allocated group.

Number of hospital visits due to asthma

- Number of hospital admissions for asthma over participant's follow-up period

- Number of emergency department attendances for asthma over participant's follow-up period

will be summarised descriptively with the number and percentage of participants reporting any events in each allocated group. The number of events will also be categorised as 1, 2, or >2.

ACQ5

ACQ5 score will be analysed using mixed-effect linear regression model adjusting for minimisation factors, baseline ACQ5 score, and follow-up duration for ACQ5 with GP practice as a random effect. The adjusted difference in means between groups will be estimated along with a 95% confidence interval.

ACQ5 score will be summarised in each allocated group using mean, median, lower & upper quartiles, minimum, maximum and number of observations according to the follow-up duration for ACQ5.

7 ANALYSIS OF SAFETY

7.1 Adverse events

Targeted adverse events (palpitations, pneumonia, and oral thrush) will be collected. The number of participants who reported at least one targeted adverse event in each allocated group will be presented. Additionally, for each targeted adverse event, the number of participants who reported it at least once and the total number of times each participant reported it will be presented.

Serious adverse events will be summarised by presenting the total number of serious adverse events, the types of serious adverse events, and the number of participants who reported at least one serious adverse event.

8 FINAL REPORT TABLES, FIGURES AND LISTINGS

2003 RELIEF Dummy Tables Final v2.0_01Oct2025

9 REFERENCES

1. McKeever T, Mortimer K, Wilson A, Walker S, Brightling C, Skeggs A, et al. Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. 2018.
2. Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. The Lancet (British edition). 2019;394(10202):919-28.
3. Asthma: diagnosis, monitoring and chronic asthma management 2017 [Available from: https://www.nice.org.uk/guidance/ng80/evidence/chronic-asthma-management-pdf7079863934.
4. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma. The New England journal of medicine. 2018;378(20):1865-76.
5. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma. The New England journal of medicine. 2018;378(20):1877-87.

6. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma. The New England journal of medicine. 2019;380(21):2020-30.