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

Health Economic Analysis Plan (HEAP)

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Sign off:

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Contents

1.Trial Summary

Table 1: Synopsis of protocolled 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 evaluate 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. Participants will be followed up to March 2025.

2. Purpose

The aim of this Health Economics Analysis Plan (HEAP) is to prospectively outline the design and methods used to evaluate the cost effectiveness of replacing short-acting beta agonists (SABA) inhalers, containing Salbutamol, with inhalers containing ICS/formoterol in patients with mild asthma using data from the RELIEF trial.

The methods specified here are an indicative guide for the economic analysis of the RELIEF trial and are subject to change in accordance with amendments to relevant guidelines (1,2) and the completion rates of health economic measures within the trial.

3. Economic Perspective

The primary analysis will adopt a National Health Service (NHS) and Personal Social Services (PSS) perspective, in accordance with National Institute for Health and Care Excellence (NICE) guidance (2). A secondary analysis will take a broader societal perspective, incorporating costs like time lost from employment, out-of-pocket expenses, and informal care.

4 Data and Management

4.1 Software

Economic data will be extracted directly from the study database as raw Microsoft Excel files and then subsequently imported and analysed using StataSE 18 (StataCorp, USA).

4.2 Data Cleaning

Plausibility checks will be performed on economic data, including range and consistency checks for variables relevant to the health economic analysis. Data queries will be addressed by clarifying with data management or site staff where necessary. Assumptions necessary for compiling the dataset that may impact study findings will be explicitly stated in reporting.

5. Economic Data and Management

5.1 Outcomes

The primary outcome for the cost effectiveness analysis will be the quality-adjusted life year (QALYs), a generic measure of health that combines both longevity and health-related quality of life (HRQoL)(3). One QALY equates to one year of life in perfect health. In this study, HRQoL will be measured using the EQ-5D-5L instrument, a validated and widely used tool for capturing patient-reported health status. Responses to the EQ-5D-5L questionnaires at baseline, and at 3, 6, 9, and 12 months follow-up will be reported descriptively (4).

HRQoL scores associated with participant EQ-5D-5L defined health-state profiles will be derived using the established English EQ-5D-5L value set (5), and in line with current NICE guidance, separately calculated using a published mapping of EQ-5D-5L responses onto EQ-5D-3L preference scores (6). QALYs will be derived using an area under the curve (AUC) approach with linear interpolation between HRQoL assessments.

Scores from the EQ-VAS (visual analogue scale for self-reported health status) will be descriptively presented alongside preference scores from the EQ-5D descriptive system. EQ-VAS scores will be divided by 100 to aid cross comparison.

5.2 Resource Use and Costs

Data from a purposively designed patient resource proforma collected participant-level resource information on aesthma-related aspects of participants' treatment and follow-up, including medication, inpatient and outpatient hospital visits, and primary, social and community care resource use at 3,6,9 and 12 months. The form has further been designed to capture emergency ambulance use, travel, informal care, and productivity losses due to time off work.

5.3 Costs

Unit costs for health care resource use and broader societal factors will be taken from the trial and a variety of national sources, including:

- NHS Reference Costs (7): Inpatient and outpatient visits.
- Unit Costs of Health and Social Care (PSSRU) (8): Primary and community services.
- British National Formulary (BNF) (9): Medication costs.
- The Annual Survey of Hours and Earnings (ASHE) (10): Productivity costs

Out-of-pocket expenses and travel costs will be derived directly from self-reported data.

The intervention-specific costs will focus on the use of ICS/formoterol inhalers, specifically Fostair 100/6 or Symbicort 100/6, as replacements for the traditional SABA inhaler. Each inhaler's unit price will be included in the costing analysis based on standard list prices recorded within the BNF (9). The total intervention cost will be calculated based on the observed number of relevant inhalers prescribed to each patient throughout the study. Intervention costs will be calculated on an intention-to-treat (ITT) basis and assume full usage or wastage of prescribed inhalers. By tracking prescription data, we will determine individualised costs for each participant, accounting for variations in inhaler usage across the trial cohort.

6. Procedures for Missing Data

The handling of missing economic data will adhere to the intention-to-treat principles. Multiple Imputation of Chained Equations (MICE) will be used to address gaps in participant-level resource use and HRQoL data (11). This method uses regression techniques to estimate missing values based on the available data. Cost categories and EQ-5D preference scores will be imputed jointly. Imputed HRQoL and costs will be calculated for each treatment group with adjustments made to relevant trial design factors, clinical outcomes and baseline characteristics. Imputed values will be kept within their natural bounds by using predictive mean matching. All multiply imputed data will be analysed using Rubin's rules with the number of datasets proportional to the overall degree of missingness (12).

7. Within-trial Analysis

7.1 Population and Time Horizon

The economic evaluation will use an incremental approach between the two study groups using an intention-to-treat (ITT) population over a 6-month time horizon.

NOTE: Due to the unexpected termination of the trial by the funder, we are unable to follow all patients through to their 12-month follow-up. The primary analysis has been changed from the original protocol to use data up to the 6-month follow-up in our

primary analysis. This is intended to improve the harmony between the time horizon for our analysis and the time over which all participants were within the RELIEF study. Note fewer than 25% of patients are expected to reach the 12-month follow-up by the trial's closure. This closing plan has been approved by the funder.

7.2 Discount Rates

As the trial period is within one year, no discounting will be applied to either costs or outcomes (QALYs).

7.3 Analysis

The economic evaluation will compare costs from both the healthcare (NHS and Personal Social Services) and a broader societal perspective. Costs will be summarised within individual resource categories and in total, with aggregation conducted for each study perspective. Cost, QALY, and cost effectiveness estimates will be derived using multiply imputed data to account for missingness and enhance robustness.

Cost effectiveness will be evaluated using incremental cost effectiveness ratios (ICERs) and incremental net monetary benefits (INMBs). For the base-case analysis, differences in costs and outcomes between trial arms will be estimated via seemingly unrelated regression (SUR) models using imputed datasets. This approach allows for simultaneous estimation of cost and QALY equations, accounting for potential correlation between error terms while adjusting for baseline and other covariates (13).

Regression models will estimate treatment-specific cost and QALYs while adjusting for site identifier, participant age, and sex amongst other potentially relevant trial variables. To account for potential baseline imbalances in health-related quality of life, QALY regressions will also include baseline EQ-5D preference scores as a covariate (14).

7.4 Sensitivity Analysis

Uncertainty surrounding the estimated treatment effects will be addressed through probabilistic sensitivity analysis (PSA). This will involve simulating the joint distribution of regression coefficients using 10,000 Monte Carlo iterations, under the assumption of multivariate normality (15). This approach will enable us to quantify how uncertainty in both costs and outcomes translates into the likelihood of overall cost effectiveness.

Findings from the PSA will be illustrated on the cost-effectiveness plane, showing the joint distribution of incremental costs and QALYs. In addition, cost effectiveness acceptability curves (CEACs) will be generated using the net monetary benefit (NMB) framework (16). This method expresses the value of the intervention in monetary terms, relative to a specified willingness-to-pay threshold (λ) per QALY. The health economic

analysis will consider the range of cost effectiveness thresholds adopted by NICE (£20,000–30,000 per QALY gain) (2).

The incremental net monetary benefit (INMB) will be calculated as:

$$INMB = (\lambda * \Delta Outcome) - (Cost_{Intervention} - Cost_{TAU})$$

This formulation is derived from the conventional decision rule: an intervention is considered cost effective if the ICER falls below the threshold value (λ). Equivalently, an intervention is cost effective if it's INMB is greater than zero at a given threshold value (λ).

We will calculate INMBs across a range of λ values to reflect varying decision-maker willingness-to-pay thresholds. The CEAC will then present the probability (from 0% to 100%) that the intervention is cost effective at each threshold, providing a more comprehensive assessment of decision uncertainty.

7.4 Scenario Analyses

Scenario analyses will be conducted to explore the impact structural and methodological assumptions have on base case findings. Scenarios will consider a complete case analysis, the use of EQ-5D-5L preference values in the calculation of QALYs (5), unadjusted (observed) estimates of costs and outcomes, and, if possible, the inclusions of 12-month follow-up data in the analysis. Should assumptions arise during our analysis that influence costs or outcomes, we will conduct scenario analyses to assess their potential implications on study findings.

8. Modelling

The original protocol outlined developing a Markov economic decision model to estimate lifetime costs and outcomes (provided sufficient data were available). However, early termination of the trial has made this unfeasible with recruitment 50% below the original target, and with only 10% of the intended sample size having 12-month follow-up data. This has been approved by the funder in the closing plan.

9. Reporting

9.1 Reporting Standards

The reporting of our findings will include a CHEERS checklist and will be submitted for peer review and form part of the main publication and synopsis (1).

9.2 Deviations

Any deviations from the HEAP will be reported in full and communicated with the study team.

10. References

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11. Appendices

Example Table 1: Imputed VAS, QALY and HRQoL preference scores and estimated QALYs at 6 months

	ICS/formoterol Mean (SE)	SABA Mean (SE)	Difference in means between groups (SE)
Average imputed values			
EQ-VAS (scaled)			
EQ-5D-5L			
EQ-5D-3L (mapped)			
QALYs			
Estimated values			
QALYs			

SE: standard error

Example Table 2: Average imputed costs per patient and difference in means between groups at 6 months

	ICS/formoterol		SABA		Difference in means between groups (£)
	Mean (£)	SE	Mean (£)	SE	Mean (SE)
Health service perspective					
Intervention cost					
Inpatient services					
Outpatient services					
Primary and community care					
Broader societal perspective					
Informal care					
Productivity costs					
Travel					
Total costs					
Health Service Perspective					
Societal Perspective					

Example Table 3 Cost Effectiveness Results

	Costs (95% CI)	QALYs (95% CI)	Incremental costs (95% CI)	Incremental QALYs (95% CI)	**ICER**
NHS perspective					
SABA			-	-	-
ICS/formoterol					
Societal perspective					
SABA			-	-	-
ICS/formoterol					

CI: Credible interval; ICER: Incremental Cost-Effectiveness Ratio

Example Table 4 Incremental Net Monetary Benefit Results

	ICS/formoterol versus SABA					
WTP thresholds (λ)	£1,000	£10,000	£20,000	£30,000	£40,000	£50,000
iNMB						

INMB: Incremental Net Monetary Benefit; WTP: Willingness-to-pay