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

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SYNOPSIS

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.
Health economics	**Objectives** To determine the resource implication of the intervention compared to usual care from a health and societal perspective. To determine whether the intervention is cost effective compared to usual care. **Outcomes** Quality-adjusted life years EQ-5D-5L as a measure of patient health-related quality of life Exacerbations of asthma **Resource Use** Data will be collected on health care resource use and social care using a purposely designed Health Economic Resource Proforma **Analysis:** Cost utility analysis (CUA), Cost effectiveness analysis (CEA) The costs and benefits will be analysed using Marginal Net Benefit approach and Cost Effectiveness planes. Cost effectiveness acceptability curves will be determined between the control and the intervention group. Economic Modelling of life course effects
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

	• Health-related quality of life: EQ5D-5I at baseline, 3, 6 9 and 12 months
Statistical methods	**The primary outcome:** Cox proportional hazard model adjusting for minimisation factors will be used to estimate hazard ratio and 95% confidence interval for the between group comparison. Participants will be analysed according to randomised group regardless of their adherence to the allocated treatment. **Secondary outcomes**: Appropriate regression models will be used, depending on the type of variable, adjusting for minimisation factors.
Qualitative study analysis	Qualitative data will be analysed using an inductive thematic approach in line with the Braun and Clark methodology.

ABBREVIATIONS

ADR	Adverse Drug Reaction
ACQ5	Asthma Control Questionnaire
AE	Adverse event
BTS/SIGN	British Thoracic Society & Scottish Intercollegiate Guidelines Network
CI	Chief Investigator
CEA	Cost Effectiveness Analysis
COPD	Chronic Obstructive Pulmonary Disease
CUA	Cost Utility Analysis
CRF	Case Report Form
CRN	Clinical Research Network
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSUR	Development Safety Update Report
eCRF	electronic Case Report Form
EOT	End of Trial
EQ-5D-5L	EuroQol-5 Dimension-5 Levels Questionnaire
CNSGP	Clinical Negligence Scheme for General Practice
GINA	Global Initiative for Asthma
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
IMP	Investigational Medicinal Product

IUD	Intrauterine Device
IUS	Intrauterine System
LABA	Long-Acting Beta-Agonists
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NRAD	National Review of Asthma Deaths
NRES	National Research Ethics Service
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
QOL	Quality of Life
REC	Research Ethics Committee
R&D	Research and Development department
SABA	Short-Acting Beta-Agonists
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study within a Trial
TMG	Trial Management Group
TAU	Treatment As Usual
TSC	Trial Steering Committee
UON	University of Nottingham

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TRIAL BACKGROUND INFORMATION AND RATIONALE

Asthma is a common, inflammatory condition of the airways, affecting approximately 10% of adults in the UK [1]. Approximately half of those affected have relatively mild asthma [2] but despite being described as “mild”, these patients experience unnecessary morbidity and avoidable mortality. Many patients with mild asthma have poor asthma control and up to 15% have a severe attack each year [2]. Moreover, 14% of the 155 people who died in the UK as reported in the National Review of Asthma Deaths (NRAD) were being treated for mild asthma [3]. A recent taskforce on severe exacerbations in asthma among adults stated that “any patient with asthma may suffer a severe exacerbation and even die from one; in fact, most exacerbations present in mild asthmatics, who are the majority of asthma sufferers” [4].

Mild asthma does not have a formal definition but is generally accepted to be patients requiring no more than low dose inhaled corticosteroid (ICS) maintenance treatment with a short-acting beta-agonist (SABA) for symptom relief [5]. SABAs have no anti-inflammatory activity and a series of studies in the 1980s [6] suggested they may actually worsen airway inflammation and asthma control if taken regularly without ICS treatment; explaining why they are prescribed on an “as needed” basis. In an attempt to improve the treatment of mild asthma, the threshold for starting patients on ICS treatment has reduced over time and the most recent version of the British Thoracic Society & Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guidelines [5] recommended treatment with ICS from the point of diagnosis for all patients with confirmed asthma requiring SABA three times a week or more. Unfortunately, prescribing data show that while there has been a small increase in patients with asthma on low dose ICS between 2015 and 2019 there has also been a small increase in patients on SABAs only [2]. Furthermore, even when patients are prescribed an ICS, there is considerable data to show that adherence with this treatment is very poor despite many decades of asthma education [7].

Unfortunately, many patients are, therefore relying on their SABA at the expense of ICS treatment, a pattern of use known to be associated with asthma deaths in epidemiology studies [8, 9] and in NRAD [3]. More recently, increasing use of SABA canisters has been associated with increased risk of asthma exacerbations in the UK and elsewhere in the world. Asthma exacerbations are not only frightening for patients but require treatment with oral corticosteroids which have unpleasant and serious adverse effects [29]. Heat maps have been generated highlighting areas of England where high use of SABAs and asthma exacerbations are particularly problematic.

In December 2019 and based on two studies described below, Global Initiative for Asthma (GINA)[10], took the bold and controversial step of recommending the replacement of SABA inhalers as the first choice for symptom relief with a combination inhaler containing both an ICS and the quick onset, long-acting beta-agonist (LABA) formoterol for patients with asthma of all severities. This included patients with mild asthma (figure 1), even though they admit some of the data was only inferred from patients with more severe asthma. Step 1 recommends ICS/formoterol as required with no maintenance treatment and step 2 recommends ICS/formoterol as required either alone, or with low dose ICS maintenance treatment, even though this combination has never been studied in a clinical trial.

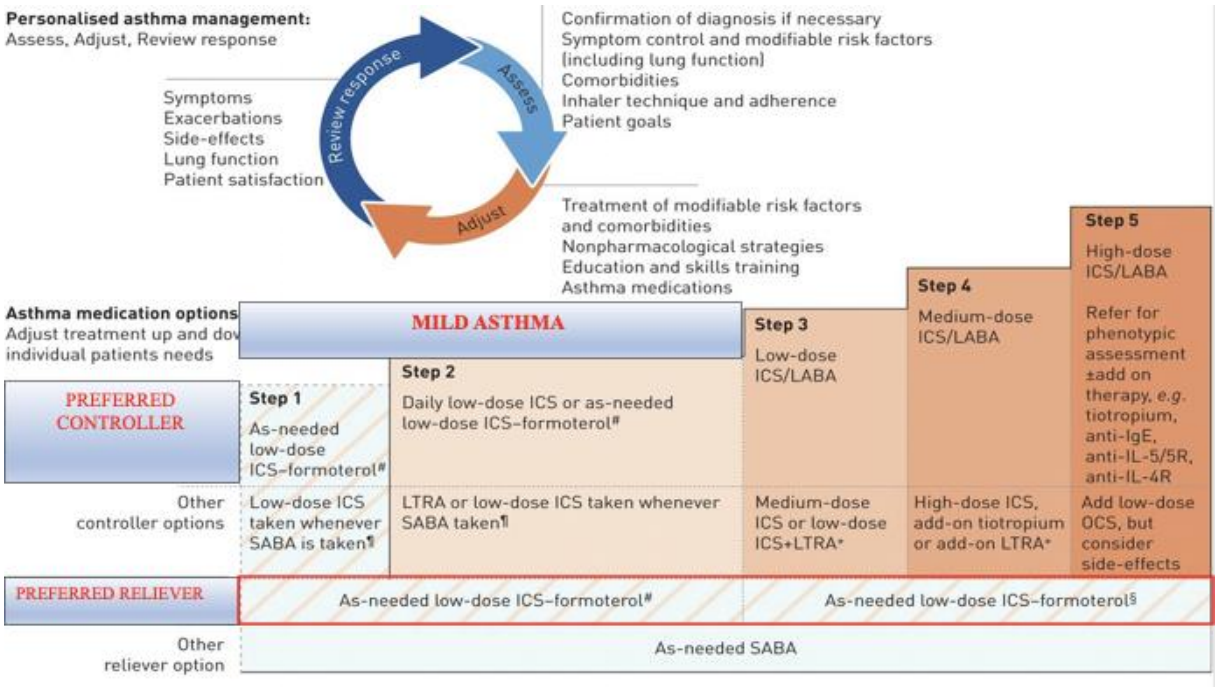


Figure 1: Treatment summary from GINA 2019 [10]. N.B. Red highlights show changes to preferred controller/maintenance and reliever therapy in mild asthma.

Switching the relief inhaler from a SABA to a combined ICS/formoterol inhaler so that patients receive ICS each time they use their relief inhaler, could potentially reduce asthma exacerbations and deaths from mild asthma. This is because: 1) patients who stop using their maintenance ICS regularly will still receive ICS each time they use their relief medication and 2) when asthma control worsens, the dose of ICS received will increase through relief medication use. To date, two large regulatory studies in mild asthma [11, 12] have shown clear benefit from ICS/formoterol as required for symptom relief versus SABA alone, but more modest benefit compared with low dose maintenance ICS plus SABA for symptom relief. Two pragmatic studies in mild asthma [13, 14] showed benefit from ICS/formoterol versus SABA alone and maintenance ICS with SABA but they were relatively modest in size and did not include a health economic evaluation. However, based on these data, the GINA strategy replaced SABA as required with ICS/formoterol as required as the first-choice reliever, across the whole range of asthma severity [10].

There remain major evidence gaps and concerns about this approach within primary care that must be addressed. These include:

1) At step 2 of the new GINA strategy (Figure 1) there is a choice between (a) combination ICS/formoterol as required for symptom relief and no maintenance treatment, or (b) low dose ICS maintenance plus combination ICS/formoterol as required for symptom relief. The first of these options has been evaluated in the studies described above but the European Regulator declined a licence for as required ICS/formoterol alone because they deemed it inferior to low dose maintenance ICS (if taken regularly). It has also caused concern in UK primary care because it goes against the dogma that regular treatment with ICS is the best way to manage asthma. The second option of maintenance ICS plus ICS/formoterol as required, can be

argued, is likely to lead to the best asthma control overall (ICS for daily control and ICS/formoterol as required, for exacerbations) but, to date, this combination has not been evaluated in a clinical trial.

2) Many patients treated for asthma have no objective evidence of a diagnosis when formally evaluated [15, 18]. If these patients are switched to a combination of ICS/formoterol for symptom relief, there is a real risk that they will use high doses of ICS/formoterol with no clinical benefit and risk of adverse effects. This potential risk needs to be evaluated in a pragmatic trial before creeping into clinical practice.

3) There is no economic evaluation of this new approach, which is particularly important because combination ICS/formoterol for symptom relief is considerably more expensive than SABAs. However, asthma exacerbations leading to unscheduled health care costs and admissions to hospital are the most expensive part of asthma care.

4) There is a paucity of data on health care professionals' and patients' views on this fundamental change in asthma management. The SABA inhaler has been around for over 50 years, so many patients and doctors are likely to be reluctant to change. We need to understand the potential barriers and facilitators to change if this recommendation is going to be considered for routine health care.

The overall aim of this trial is to determine the clinical benefit, cost effectiveness, physician, and patient perspective of replacing SABA with an ICS/formoterol containing inhaler in patients with mild asthma, treated with low dose ICS, before this approach creeps into UK clinical practice without us knowing the consequences. Replacing SABAs represents a fundamental change in asthma management and as such we also plan a detailed qualitative study exploring the beliefs of patients, and health care providers, throughout the trial.

DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Participants will be randomised to an "as required" combination ICS/formoterol, or to an "as required" SABA (salbutamol) for symptom relief. Each preparation will be prescribed in accordance with the manufacturer's instructions when used as maintenance and relief therapy. In the UK ICS/formoterol is typically available as Symbicort® 100/6 or Fostair®, 100/6, and both are licensed for 'as required' use in moderate to severe asthma. All participants in the trial will continue to receive low dose ICS in accordance with standard practice (e.g. see exemplar below) and is considered to be a nIMP (non-investigational medicinal product) in this trial.

Please note that there are other generic names available for these prescribed medications. The IMPs are defined by their active substances only and all available brands and forms can be prescribed. However, the active ingredients that make up these prescribed medications will be identical to those described below.

Descriptions

Combination ICS/formoterol (Experimental)

One of two combinations may be used either,

1) Beclometasone dipropionate, formoterol fumarate dihydrate

Each metered dose (ex-valve) contains: between 100 and 200 micrograms of Beclometasone dipropionate and 6 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of 84.6-169.2 micrograms of Beclometasone dipropionate and 5.0 micrograms of formoterol fumarate dehydrate. One inhalation as required, for relief of symptoms; maximum 8 inhalations per day.

Please refer to the Fostair® 100/6 SmPC, provided as an example, for detailed information on the drug's chemical and pharmacological properties.

Common side effects

Headache; oral candidiasis; pneumonia (in patients with COPD); altered taste; voice alteration.

A full list of known side effects is detailed in the exemplar SmPC patient information leaflet.

Manufacturer

Fostair® 100/6 - Chiesi Limited, 333 Styal Road, Manchester, M22 5LG, United Kingdom. The IMP is defined by its active substance only and all available brands and forms of can be prescribed.
UK licence number: PL 08829/0156

Or

2) Budesonide, formoterol fumarate dihydrate

Each metered dose contains budesonide 100-400 micrograms/inhalation and formoterol fumarate dihydrate 4.5-12 micrograms/inhalation.

Excipient with known effect - lactose monohydrate 810 micrograms per delivered dose.

Initially: 1–2 puffs twice daily, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained. Asthma, maintenance, and reliever therapy by inhalation of powder

Maintenance: 2 puffs daily in 1–2 divided doses; 1 puff as required for relief of symptoms, increased if necessary, up to 6 puffs as required, max. 8 puffs per day; up to 12 puffs daily can be used for a limited time but medical assessment is recommended.
Please refer to the Symbicort® 100/6 SmPC, provided as an example, for detailed information on the drug's chemical and pharmacological properties.

Common side effects

Arrhythmias; headache; palpitations; tremor.
A full list of known side effects is detailed in the exemplar SmPC patient information leaflet.

N.B. Hypersensitivity to lactose is a contraindication.

Manufacturer

Symbicort® 100/6 - AstraZeneca UK Limited, 600 Capability Green, Luton, LU1 3LU, United Kingdom. The IMP is defined by its active substance only and all available brands and forms of can be prescribed.
UK licence number: PL 17901/0091.

Short acting beta agonist (Comparator)

Salbutamol sulfate

Each dose of Salbutamol contains 100 microgram of Salbutamol sulfate per 1 metered dose100–200 micrograms, up to 4 times a day for persistent symptoms.

Please refer to the Easyhaler Salbutamol® SmPC, provided as an example, for detailed information on the drug's chemical and pharmacological properties.

Common side effects

Arrhythmias; headache; palpitations; tremor
A full list of known side effects is detailed in the SMPC patient information leaflet.

Manufacturer

Easyhaler Salbutamol® - GlaxoSmithKline UK Limited Registered in England and Wales No 4310159. Registered office: 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom. The IMP is defined by its active substance only and all available brands and forms of can be prescribed.
UK licence number: PL 10949/0274

Beclometasone Dipropionate (non-investigational medicinal product (nIMP))

Beclometasone Dipropionate dose for prophylaxis of asthma is 200–400 micrograms twice daily; increased if necessary up to 800 micrograms twice daily, dose to be adjusted as necessary.

Please refer to the Easyhaler Beclometasone® SmPC, provided as an example, for detailed information on the drug's chemical and pharmacological properties, but any brand can be used.

Common side effects

Headache; oral candidiasis; pneumonia (in patients with COPD); altered taste; voice alteration. A full list of known side effects is detailed in the SmPC patient information leaflet.

Manufacturer

Easyhaler Beclometasone® - Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, United Kingdom. The nIMP is defined by its active substance only and all available brands and forms of can be prescribed.
UK licence number: PL 00289/1374
Packaging and labelling

In accordance with the Medicines and Healthcare products Regulatory Agency (MHRA) risk-adapted approach to the management of clinical trials of investigational medicinal products [32], and the pragmatic nature of the trial, this trial will not require trial specific labelling. While the trial is considered a Type B trial, all asthma treatments being used in this trial are established treatments with well documented safety profiles. The inhalers used in the trial are "off the shelf" and are widely prescribed in primary care. Whilst the test arm is being used outside its licenced indication, this relates only to the degree to which the patients are suffering from asthma. This use is already established practice for moderate to severe asthma and supported by published guidelines [32], this trial is merely extending the patient cohort to specifically include those patients with "mild" asthma. No new side effects are anticipated and the risk to patients is therefore low.

Storage, dispensing and return

There are no trial-specific requirements for the storage of any of the treatments used in this trial. All treatment prescribed and dispensed for the purpose of the trial will originate from standard pharmacy stock which will be stored in accordance with the manufacturer's storage instructions as detailed in the applicable Summary of Product Characteristics (SmPC). Sites and/or local pharmacies will follow their own local policies for storage of medication. There are no special instructions for storage of dispensed products once with the patient and no returns are anticipated.

Placebo

There is no placebo associated with this trial.

Known Side Effects

Common side effects are detailed above for each drug preparation. Full details of side effects are available in the example SmPCs.

Reference Safety Information:

This will be section 4.8 of the following SmPCs;

Fostair 100/6 micrograms per actuation pressurised inhalation solution, updated 3rd Mar 2020
Symbicort Turbohaler 100/6, Inhalation powder, updated7th Jan 2021.
Easyhaler Salbutamol 100 micrograms per actuation pressurised inhalation solution, updated 06 Sept 2020.
Easyhaler Beclometasone 200 micrograms per actuation, updated 14th Feb 2022.

TRIAL OBJECTIVES AND PURPOSE

PURPOSE

The overall aim is to determine the clinical and cost effectiveness of replacing Salbutamol inhalers with inhalers containing ICS/formoterol for symptom relief in patients with asthma treated with low dose ICS maintenance treatment. Our hypothesis is that using a combination of ICS/formoterol instead of Salbutamol for symptom relief will reduce asthma exacerbations because it provides more ICS when needed and overcomes the common problem of poor adherence with maintenance ICS treatment.

A qualitative sub-study will investigate the acceptability of the intervention.

We will be conducting a 'study within a trial' (SWAT)to investigate the effects of an intervention package to improve inclusivity in the trial. (Please see SWAT section for details).

PRIMARY OBJECTIVE

- To compare the time to first severe exacerbation (defined as treatment with 3 or more days of systemic corticosteroids) in patients using regular low dose ICS and randomised to either 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: EQ5D-5I at baseline, 3, 6 9 and 12 months.

TRIAL DESIGN

TRIAL CONFIGURATION

A pragmatic, open label, randomised controlled trial with an internal pilot. The trial is a multicentre trial that will recruit 2,300 people with a clinical diagnosis of mild asthma, treated with low dose ICS with Salbutamol as required.

Potential participants will be identified from each primary care practice from primary care records or by direct invitation during a consultation or asthma review and recruited over approximately a 2-3 month period for any given practice. With separate practices being opened to recruitment over a period of time, the total recruitment period for the trial is estimated at 18 months. Potential participants will be invited by letter or Accurx text message. There will be a maximum number of 3 contacts for each potential participant contacted by Accurx text

messages. In addition, if sites experience a low response rate, they will have the option to call potential participants to ask if they received the invitation letter or text message. Sites will be required to use approved patient communications for all patient facing contact.

Where patients are identified as initially ineligible because they are not currently receiving low dose ICS, they may be approached to the enter the trial should they subsequently be prescribed low dose ICS by their GP as part of their standard care and have received at least 1 month of low dose ICS.

Participants will then be randomised 1:1 to one year of ICS/formoterol or Salbutamol as required for symptoms whilst continuing their low dose ICS maintenance therapy. Participants will be reviewed in clinic, or remotely by telephone consultation, at 1 and 12 months and contacted by text, monthly, to collect primary outcome data. The trial will have an embedded health economic analysis and qualitative study. This will incorporate a full economic evaluation and a qualitative study of patient and health care practitioners' experiences and views of this alternative approach to asthma management.

Primary endpoint

The primary outcome is time to first severe exacerbation, defined as having taken treatment with systemic corticosteroids for an asthma worsening for at least 3 days. This endpoint has been chosen because severe exacerbations is a common outcome in clinical trials, defined in the American Thoracic Society/European Respiratory Society statement on standardising endpoints in clinical trials in asthma [19] and recommended as a core outcome in National Institute of Health task group [20].

Secondary endpoints

- Number of severe asthma exacerbations over a 12-month period post-randomisation
- 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 in the 12 months post randomisation
- ACQ5 symptom questionnaire at 12 months post-randomisation
- Acceptability of new treatment will be assessed via an embedded qualitative study
- Health-related quality of life: EQ5D-5I at baseline, 3, 6, 9 and 12 months

Qualitative Study

Alongside the main trial, a selection of the recruited participants will be approached to participate in qualitative interviews. There will also be interviews with healthcare professionals (e.g. GPs and asthma nurse specialists in primary care).

The aim of the qualitative study is to explore in depth patient and healthcare professional experiences, education and understanding of their asthma treatment and their experiences of the treatment regimen they have been randomised to.

Qualitative exploration outcomes

A synthesis of the qualitative data will be conducted using a thematic approach with the aim of producing a thematic framework map which will explore:

- Education / knowledge of the participants
- Experience of the treatment regimen
- Barriers to the treatment regimen
- Facilitators to the treatment regimen
- Acceptability of the treatment regimen
- Practical / ethical implementation of the treatment regimen
- Change in knowledge / attitude over the course of the treatment regimen

Safety endpoints

Given the low-risk nature of this trial, we will adopt a targeted approach to Adverse Event (AE) and Serious Adverse Event (SAE) reporting. We will exclude AEs due to disease progression in this protocol. However, if participants report experiencing palpitations, pneumonia and/or oral thrush to their GP/research team these will be logged as an AE and reported as described in ADVERSE EVENTS. Where these events meet the definition of "Serious" they will be reported in the annual DSUR.

Please note: data on exacerbations of asthma symptoms serious enough to require intervention (typically prescribed oral steroids) will be collected monthly as the primary outcome measure of the trial.

AEs which are Serious should be reported in an expedited manner via an SAE Form (see ADVERSE EVENTS section). Participants will report serious adverse events to the research team and sites will forward these to NCTU within 24hrs of the Practice being made aware of the event, if the Practice isn't already aware of the event via other means, such as hospital discharge letters, so they can be reviewed, categorised and reported.

Stopping rules and discontinuation

There is no formal interim analysis of treatment effectiveness planned.

Recruitment will be assessed following the internal pilot phase (see below for further details) to determine the feasibility of recruitment according to agreed progression criteria. The review will be undertaken by the Trial Management Group (TMG) and Trial Steering Committee (TSC) and if recruitment figures meet the red or amber categories, additional strategies will be put in place to attempt to improve these.

Internal pilot

The trial will contain an internal pilot phase that will test the recruitment of sites and participants against agreed milestones. The pilot will be examined 18 months after the grant commences (covering the 9 months set up, 8 months recruitment and 1-month internal pilot progression criteria analysis). Table 1 below denotes the progression criteria, along with actions that will be undertaken for each category.

Table 1: Internal pilot progression criteria

	Black	Red	Amber	Green
% Threshold	<35%	35-79%	80-99%	100%
Number of active sites	18 or fewer	19 - 42	43 - 52	53
Number of randomised participants	347	348 - 796	797-995	996
Action	Consider stopping the trial	Continue, with recovery plan agreed with TSC and HTA	Continue, action needed	Continue, no action needed

It is important to note there will be no break in recruitment unless the stopping criteria are met.

Decision to proceed or stop the trial

The TSC will review the data on recruitment from the internal pilot and make recommendations to the TMG. The above criteria (Table 1) will aid decision making about progression of the trial, although final agreement on stop/go criteria will take place after discussion with the HTA.

The Sponsor also reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and the funder (NIHR HTA) as appropriate in making this decision.

RANDOMISATION AND BLINDING

Enrolment:

(a) Throughout the trial, screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for non-participation or exclusion. At visit 1, and following informed consent, participants will complete the Asthma Control Questionnaire (ACQ5) [17], EQ-5D-5L [18] and a questionnaire to collect health resource use data.

(b) Qualitative sub-group. The patients in the main trial will be asked if they are willing to participate in the qualitative sub-study when they are approached for enrolment into the main trial. Only a sub-set of these patients will subsequently be approached to participate. Additionally, a number of healthcare professionals associated with the trial will be approached to participate in the qualitative element of the study.

Randomisation:

All participants consenting to the main 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.

The exact choice of ICS/formoterol or Salbutamol will be left to GP discretion. The following IMPs are indicative of the treatment options available; however a generic equivalent may be prescribed:

- Fostair 100/6 micrograms per actuation pressurised inhalation solution.
- Symbicort Turbohaler 100/6, Inhalation powder
- Ventolin Evohaler 100 micrograms

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.

Maintenance of randomisation codes and procedures for breaking code

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.

TRIAL MANAGEMENT

The TSC will meet at least once a year or as required and will provide independent oversight of the trial on behalf of the trial sponsor. The sponsor will be invited to all TSC meetings for the trial as an Observer. The Data Monitoring Committee (DMC) will meet at least once a year or as required to assess safety, effectiveness and futility of the trial and will report to the TSC. The TMG will meet more frequently, at least every two months, and will be responsible for the day-to-day management of the trial. The Chief Investigator has overall responsibility for the trial and shall oversee all trial management. The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL AND PARTICIPANT INVOLVEMENT

The total duration of the trial will be 44 months of which the rapid recruitment period for each site in the trial is anticipated to be approximately 2-3 months. Participant follow-up will continue for a maximum of 12 months following the end of recruitment. However, recruitment progress and timelines will be monitored against projected recruitment and overall timelines will be adjusted if considered necessary.

End of the Trial

The end of trial will be the date of the final database lock.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Recruitment will be from primary care GP practices across England, Scotland and Wales. The Primary Care Clinical Research Network (CRN) and the NIHR Identity Gateway will be used to identify practices with a good track record for recruitment, including participation in relevant studies such as FAST and TWICKS [28]. It is estimated needing a minimum of 100+ practices to recruit 2,300 participants over 18 months. In addition, potential participants' can make contact with their GP, or the research team, as a result of trial advertising and promotional material (e.g. posters, leaflets, NCTU and social media). Upon initial contact participants will be signposted to their GP practice and can be informed that they can only be involved if their GP practice is a host site. Please note that the devolved nations Wales and Scotland are not part of the Clinical Research Network. In Wales, recruitment is supported by R&D Wales; and for Scotland, the NRS Primary Care Network will support practices to identify, invite and manage patients in the trial for Scotland.
In conjunction with the CRN, a screening tool that will generate lists of all potentially eligible patients at GP practices will be developed. Only GP practice staff will have access to this list. The resultant screening lists will be reviewed by the GP and any ineligible patients will be excluded. Letters of invitation together with the PIS and a reply slip will be sent to all eligible participants over a 2-3 month period to ensure that the GP practice can manage the responses in a timely manner. Some sites may prefer to use AccurX to recruit participants, however only approved language and links to the invitation letter and PIS will be used for this purpose.

On receipt of the reply slips/responsesa site staff member will contact the potential participant to discuss the trial and answer any questions they may have. If potential participants indicate they would like to enter the trial a consent/baseline appointment will be made.

Potential participants may also be approached during a routine asthma screening appointment. If interested, they will be given a PIS to read and given the opportunity to ask questions. Participants can take the PIS away and return a reply slip to be contacted further. Alternatively, if time allows, interested participants will be given the opportunity to complete the reply slip and continue to the consent process within the GP consultation. If potential participants agree to be involved at this stage a separate consent/baseline appointment (either face-to-face or remote) will be made. The consultation will be undertaken at site level by a suitably qualified member of the research team. This will provide time for the potential participant to talk through their choice with family and/or friends prior to providing written/electronic informed consent where applicable. We therefore expect sites to recruit all their participants within 3 months of opening, although if further eligible patients express an interest, the site may recruit them on an individual basis.

In accordance with the Clinical Trial Facilitation Group "recommendations related to contraception and pregnancy testing in trials", given that the IMPs are all licensed products, women of child-bearing potential can be included in the trial providing an acceptable effective method of contraception is used until treatment discontinuation.

The IMPs are licensed products which routinely prescribed to asthmatic pregnant women therefore pregnancy test will not be required before entry to the trial, but the patient should contact their GP and seek further direction if pregnancy should subsequently be confirmed.

Equality, Diversity, and Inclusion

There are areas in the UK where overuse of SABA and asthma exacerbation rates are particularly high, and these areas will be targeted for trial inclusion. Many of these areas contain communities with relatively high numbers of economically disadvantaged people and ethnic minority groups who are known to be underrepresented in asthma research.

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 COPD and clinically significant bronchiectasis).
3. Pregnancy or intention to become pregnant

Expected duration of participant participation

Trial participants will be participating in the trial for 12 months from randomisation to final follow-up.

Removal of participants from therapy or assessments

As the interventions in this trial are treatments that are widely available within the NHS, it is not anticipated that a participant would need to be removed from the trial. However, if a participants' maintenance (low dose ICS) inhaler is changed to a combined inhaler during the course of the trial, they will no longer meet the eligibility criteria. Participants will remain in the trial, and if agreeable, follow-ups will continue to be conducted for all participants regardless of whether they receive the allocated intervention or treatment as usual.

N.B. Participants who become pregnant during the course of the trial will be withdrawn from the trial and should contact their GP for further direction. The occurrence of pregnancy will be captured at site via a trial pregnancy form on the trial database. In addition, it is permissible for participants who are using birth control methods to continue in the trial as planned (acceptable methods detailed below).

Acceptable contraceptive methods include: established use of oral, injected or implanted hormonal methods; placement of an intrauterine device (IUD) or intrauterine system (IUS); condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide; true abstinence (when this is in line with the preferred and usual lifestyle of the participant); or vasectomised partner.

Treatment discontinuation

Participants who discontinue the trial treatment, or change treatment for any reason, will continue to be followed up in accordance with the trial schedule and continue to provide trial data, including completion of follow-up questionnaires for use in the analysis, unless they are unwilling to do so.

All data collected will be used, and any participants that discontinue trial treatment will be reminded of the importance of continuing to complete trial questionnaires/assessments. Reasons for trial treatment discontinuation may include participant decision, pregnancy, or significant adverse events.

Withdrawal from the trial

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time, but attempts will be made to avoid this occurrence. In the event of participant withdrawal, it will be explained that the data collected from them so far cannot be erased and will still be used in the analysis of the trial.

N.B. Data will not be erased as it should be possible to recreate a participant's participation up to their point of any withdrawal.

Participants may be withdrawn from the trial either at their own request or at the discretion of the GP/Principal Investigator (PI). Participants will be made aware (via the information sheet and consent form) of their right to withdraw. Participants can also opt to withdraw from the allocated intervention, receive an alternative treatment and continue in the trial for follow-up measures, as described at treatment discontinuation.

Withdrawal prior to randomisation

Any patients that request to withdraw their consent prior to randomisation will be withdrawn completely from the trial; they will not be randomised, and follow-up questionnaires will not be issued. The trial will continue to randomise participants until the target sample is reached, sites will be notified once this is established.

Discontinuation and withdrawal following randomisation

Everyone conducting or taking part in this trial should follow the PeRSEVERE guiding principles for clinical trial research as follows;

1) Everyone should be aware that participants may choose to change, reduce, or stop their participation after they agree to join the trial.
2) The nature and extent of participation changes should be the participant's decision to make, within the limits of what is possible for the given trial.
3) Their decision should be informed and freely given.
4) Everyone conducting or taking part in the trial should be aware that collecting as much as possible of a trial's planned data can help a trial reach a clear and reliable conclusion. Loss of contact between a participant and researchers should not be considered the same as a participant saying that they want to stop trial participation.
5) Trial data collection should continue until a trial participant explicitly tells researchers that they want it to stop.
6) Data collected for the trial up to the point a trial participant stops providing data should be used in the trial analysis and kept with the other trial data until the trial is over.
7) Stopping participation early does not affect participants' right to receive trial-related information later on, if they want to receive it or if it could be important for them to have.

The NCTU must be informed of all requests by participants to stop their involvement in the trial; appropriate action will be taken to ensure that the participant's wishes are followed. Sites will be trained to determine which activities participants may wish to withdraw from.
If site staff are made aware of a participant's withdrawal of consent for any trial activities, the PI or delegate should record this in the electronic case report form (eCRF) as soon as possible (and within 24 hours) to ensure the correct procedures are followed by NCTU and the site team. Participants will be asked their reason(s) for withdrawal but are not obliged to provide these. Withdrawn participants will not be replaced. In addition, if any significant new information becomes available regarding the treatment they received in the trial, it may be necessary to contact them in the future.

Informed consent

All participants will provide written or electronic informed consent. The Consent Form will be signed and dated by the participant (on paper or electronically where applicable) before they enter the trial. The PI (or suitable delegate) will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning trial participation. Eligibility criteria will be confirmed by the participant's GP prior to entering the trial.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination – if applicable, and history taking) related to the trial. Provision

is made for remote consent to be used should this be necessary due to issues with clinic resourcing and a lack of face-to-face provision. Consent will be obtained by a member of the site research team in accordance with the delegation of responsibilities authorised by the Principal Investigator on the site delegation log. If eConsent is to be obtained then a link to the consent form will be sent to the participant via the trial database, which will be linked to the participants unique screening record.

The REDCap eConsent framework provides advanced specialised tools to obtain consent and enables storage of consent documentation within a certification screen. The storage function automatically generates a 'hard-copy' PDF of the signed form. Participants will sign the eConsent form with a mouse, stylus, or their finger. Confirmation of consent (for those remotely recruited) will be documented in the patient medical notes and on the trial database. A copy of the signed consent form (paper or electronic) must be filed with the patient medical notes. Consent is taken following eligibility criteria confirmation and prior to randomisation at the baseline assessment. All participants will receive a PDF copy of their completed informed consent form. Participants who sign remotely will receive a copy via email and/or in the post if requested.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent Form which will be signed by the participant (see INFORMED CONSENT AND PARTICIPANT INFORMATION section for more details).

TRIAL TREATMENT AND REGIMEN

Where patients are identified as initially ineligible because they are not currently receiving low dose ICS, they may be approached to the enter the trial should they subsequently be prescribed low dose ICS by their GP as part of their standard care and have received at least 1 month of low dose ICS.
A colour-coded participant pathway flowchart illustrates details on current care and schedule of research assessments (Figure 2). A summary of research assessments is also provided in Table 2.

Assessments

Baseline

Informed consent will be obtained, when participants attend either a face-to-face or remote) baseline appointment - (assessment 1), during which the following will be collected:

- Concomitant medication checks and relevant medical history taken
- Baseline data including demographic information
- *Asthma Control Questionnaire (ACQ5) [17]
- *EQ-5D-5L [18]

- *Health economic resource use questionnaire
- Patient's employment and income status

*Questionnaires will be completed electronically unless paper copies are requested.

All participants will then be randomised 1:1, using a minimisation algorithm, to;

- as required combination ICS/formoterol for symptom relief, or
- as required Salbutamol for symptom relief

Appropriate instructions will be given in relation to the allocated medication and the initial prescription issued. Site staff should complete the Baseline CRF which includes demographic data.

Participants will not be paid to participate in the trial. However, they will be offered an inconvenience allowance consisting of a single £15 voucher, which will be given following the baseline appointment whether they are randomised or not

Follow-up

Week 1: Between days 3 & 7 following consent and randomisation, selected participants will be contacted by the qualitative team for interview if they indicated a wish to be involved on the informed consent form.

Month 1: Participants will be seen or contacted by telephone at 1 month (assessment 2) by their local GP team, as might happen in routine clinical practice after initiating a new therapy to ensure there are no problems with it. In addition, participants will be asked if they have used 3 or more consecutive days of systemic corticosteroids (predominantly prednisolone) for an asthma exacerbation since randomisation.

Months 2-11: Participants will receive a monthly automated text/email asking them if they have used 3 or more consecutive days of systemic corticosteroids (predominantly prednisolone) for an asthma exacerbation in the previous 4 weeks, with a "YES/NO" reply. A "yes" reply will be followed up with a phone call from a member of the research team at the GP site/or NCTU to confirm the use of prednisolone (or equivalent), clarification of medication and its origin if not prescribed, the dose, the date of commencement, and duration of treatment. Participants will also be asked if they have been prescribed any antibiotic treatment for their asthma in the same time period. Name of antibiotic, dose, and number of tablets prescribed will be documented.

Months 3, 6, and 9: Participants will be asked by text/email to complete the follow up questionnaires, either online or on paper if requested. An email link will be sent via the database REDCap, or by hard copy sent in the post (if requested). Questionnaires include EQ-5D-5L and a questionnaire to collect health resource use data for the health economic analysis.

Months 6 & 12: A compliance check will be carried out at month 6. GP staff will review the previous 6 months SABA inhaler prescriptions (see compliance section for more details). At

month 12 GP staff will check the 12 months medical records to retrieve the type and number of all asthma inhalers prescribed.

Month 12: At the 12-month end of trial appointment (assessment 3), which could be a face-to-face or remote appointment, the ACQ5 and EQ-5D-5L will be completed along with the final health economic resource use questionnaire before the consultation. During the consultation, GP staff will also review the previous 12 months medical records to confirm self-reported systemic corticosteroid use (predominantly prednisolone) and identify any unreported courses of corticosteroids and retrieve the type and number of all asthma inhalers prescribed (as stated in the above point).

N.B. Reminder texts and/or emails will be sent when participants do not respond to initial text enquiries or complete questionnaire data within the required period at each time point.

Qualitative procedure

Semi-structured telephone interviews with approximately 80 participants, selected to ensure geographical area coverage, pre-trial treatment, and randomised treatment arm representation, will be conducted at two or three time-points (additional time-point if an asthma exacerbation occurs or the participant chooses to stop the intervention treatment during the trial but opted to stay in the qualitative sub-study). The first interview will be at 3-7 days after participants have been placed into a treatment group and follow up interview at around 9-12 months into the trial. The interview will explore patient understanding and beliefs of their previous asthma medication regime (Salbutamol only or ICS plus Salbutamol) and their views about the medication regime they have been randomised to. These interviews will focus on patient understanding of the role of the different inhalers and their lived experience of Salbutamol use in their daily asthma control, prior to the trial.

Participants will have the opportunity to indicate their interest in being invited to interview via the optional section on the informed consent form. If the participant consents to be contacted regarding the qualitative interviews a message will be sent to the qualitative team via email. Participants will be contacted directly by the qualitative team. A telephone call will be made to participants to discuss the qualitative sub-study in detail and an appointment made to collect verbal consent followed by the interview/s. For patients being interviewed at 9 or 12 months, a copy of the PIS and consent form will be sent prior to the interview to remind the patient of the trial.

Semi-structured interviews will be repeated to explore patient experiences of their new medication regime at the end of the trial. It will be explained to the participant that additional verbal consent will be taken and recorded prior to each interview taking place. The estimated sample size of 40 participants per randomised treatment group to reach data saturation is aligned with similar qualitative studies in patient-facing asthma research which reached data saturation between 33-62 participants [23-25]. Additionally, this will ensure we have a representative sample of participants from traditionally under-represented backgrounds (e.g. ethnic minority participants), the proposed sample size should help us to ensure minority-background participants are well represented in the data set. Interviews will be recorded using UoN approved audio recording device and transcribed using UoN approved transcription services. Initial transcript analysis will take place at the time of transcription to continuously assess for data saturation, this will prevent over or under-recruitment.

In addition to these scheduled interviews, we will seek to undertake opportunistic interviews with:

1) Participants who exacerbate during the trial, to better understand their medication use and lived experiences prior to exacerbation

2) Participants who opt to stop the intervention treatment during the trial, to better understand their reasons for this.

It is anticipated that this will be a small number of participants; approximately 10-15. Semi-structured interviews will also be conducted with approximately 30 GPs and practice nurses, to understand their beliefs of replacing the Salbutamol inhaler both before and on completion of the trial to explore barriers and acceptability with the new ICS/formoterol as required regime, and how those barriers may be managed effectively. A separate PIS will be provided to site staff who will have time to read and ask questions prior to sending a reply slip to NCTU. This will be passed on to the qualitative team to make contact with interested staff and answer any questions prior to consent. The same verbal consent procedure used for participants will be used for site staff prior to any interviews taking place.

Similar studies have interviewed approximately 15 clinicians [26] however, it is acknowledged by the authors that this represents a localised geography and “not all views” may have been heard. Our research project is seeking a representative geographical sample from national recruitment and as such it is anticipated that approximately 30 clinician interviews will enable data saturation to be met with more certainty. Participants enrolled into the qualitative sub-study will receive a £30 voucher as a thank you for participating in the qualitative sub-study. This will be paid at the end of their participation in the qualitative sub-study.

We have worked extensively with our PPI group to design the qualitative interview schedule. We were particularly interested in ensuring the questions were accessible to minority groups. The PPI group will also be involved in a data analysis process called ‘member checking’, in which participants sense check the way we have coded their interviews and the themes that have been derived from them. Qualitative data will be analysed using an inductive thematic approach in line with the Braun and Clark methodology. [27]. (See Statistics section for further details).

Concomitant and Rescue Medications and Treatments

This is a pragmatic trial using medications already in use for a cohort of patients who may have other co-occurring medical conditions and be taking medication for those conditions. The trial will not collect concomitant medications except when they are thought to be a possible factor in any SAEs which are reported in an expedited manner. This will be achieved via the SAE form itself in these circumstances. There are clear pathways to escalation of treatment for asthma. Information regarding exacerbations is to be collected as part of the trial.

Compliance

All GP practices opened as sites within the trial, will review prescriptions for SABA after the first six months from randomisation. If there is evidence of ongoing requests for SABA inhalers, not in keeping with their randomisation, steps to improve site training and participant materials to better understand the new reliever and the trial will be taken for sites still recruiting participants. Updated documentation will be co-developed with the PPI group. Furthermore, if a compliance issue is identified i.e. participants in the ICS/formoterol group are still requesting SABA inhalers, monitoring of ongoing requests for SABA inhalers in participants randomised to ICS/formoterol will be extended.

Accountability for drugs & placebos

There are no trial-specific accountability requirements; sites and/or local pharmacies will follow their own local procedures for recording treatments dispensed. The number of inhalers used by each patient, over the 12-month period, will be reported by the GP practice when each participant reaches the end of the trial.

Management of trial drug overdose

For instances where an overdose of the prescribed medication occurs, this will be dealt with in line with primary care procedures. If such an event results in hospitalisation this will be captured on a SAE form and reported in the usual manner for review.

Urgent Safety Measures

If any urgent safety measures are taken the CI shall immediately and, in any event, no later than 3 days from the date the measures are taken, give written notice to the MHRA, the relevant REC and the sponsor, of the measures taken and the circumstances giving rise to those measures (more details can be found here Urgent Safety Measures). An amendment should be submitted at the earliest opportunity, should a change to trial specific procedures or the protocol be required.

Protocol Deviations and Violations

A protocol deviation can be described as any departure from the approved trial protocol.

Although adherence to the randomised treatment arm is important, we cannot prevent some patients from continuing to use SABA in the ICS/formoterol group. However, SABA prescriptions will be reviewed by all GP practices as detailed in the compliance section above. When each participant reaches the end of the trial, we plan to review medical notes for prescription for systemic steroids (the primary outcome) and prescriptions for SABA inhalers as a marker of non-adherence to the allocated treatment in the ICS/formoterol group. However, this will not be considered a protocol deviation.

A protocol violation is a divergence from the protocol that **materially** (a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare.

Protocol non-compliance will be monitored via central monitoring of eCRF data. All protocol deviations and violations will be recorded on the trial database and reviewed by the NCTU.

Criteria for terminating trial

The internal pilot review will be undertaken by the TMG, TSC and DMC, and if any of the internal pilot progression criteria fall in the red or amber categories then additional strategies will be implemented in an attempt to improve these.

Questionnaires

EQ-5D-5L: The EQ-5D-5L (8) is a validated, generalised, health related quality of life questionnaire consisting of five domains related to daily activities with five levels within each domain. The health utility index is derived by applying the country specific valuation tariff

ACQ5: The ACQ5 is a validated questionnaire to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. It comprises 5 items on symptoms in the previous week.

Resource Use: A purposively designed patient proforma will be used to collect patient resource level information. This will cover relevant items outlined in the case report forms (CRF) and will be focused and designed for the trial patient group with input from the trial patient advisory group.

Table 2: Summary of trial procedures and assessments

	Time points										
	Pre-enrolment/ screening	BL	0	3-7d	1m	2m	3m	6m	9m	11m	12m
Enrolment											
Patient identification	**X**										
Informed consent	***X**	**X**									
Confirm eligibility	**X**										
Patient demographics		**X**									
Randomisation			**X**								
Treatment/Intervention											
Salbutamol (TAU arm)			←	—	—	—	—	—	—	—	→
Low Dose ICS			←	—	—	—	—	—	—	—	→
ICS/formoterol (Test arm)			←	—	—	—	—	—	—	—	→
Medication/prescription checks								**X**			**X**
Assessments/Outcome measures											
GP follow-up & severe exacerbation enquiry					**X**						**X**
Time to 1st severe exacerbation (requiring 3 days of systemic ICS)					←	- -	- -	- -	- -	- -	→
Number of severe exacerbations (assessed via monthly text, months 2-11)						←	- -	- -	- -	→	
Number of hospital admissions for asthma					←	- -	- -	- -	- -	- -	→
Number of A&E attendances for Asthma					←	- -	- -	- -	- -	- -	→
Total prescribed SABA inhalers								X			
Total prescribed SABA, ICS & ICS/formoterol inhalers											**X**
ACQ5 questionnaire		**X**									**X**
EQ-5D-5L questionnaire		**X**					**X**	**X**	**X**		**X**
HE resource questionnaire		**X**					**X**	**X**	**X**		**X**
AE & SAE monitoring			←	- -	- -	- -	- -	- -	- -	- -	→

D = days, m = months, BL = baseline

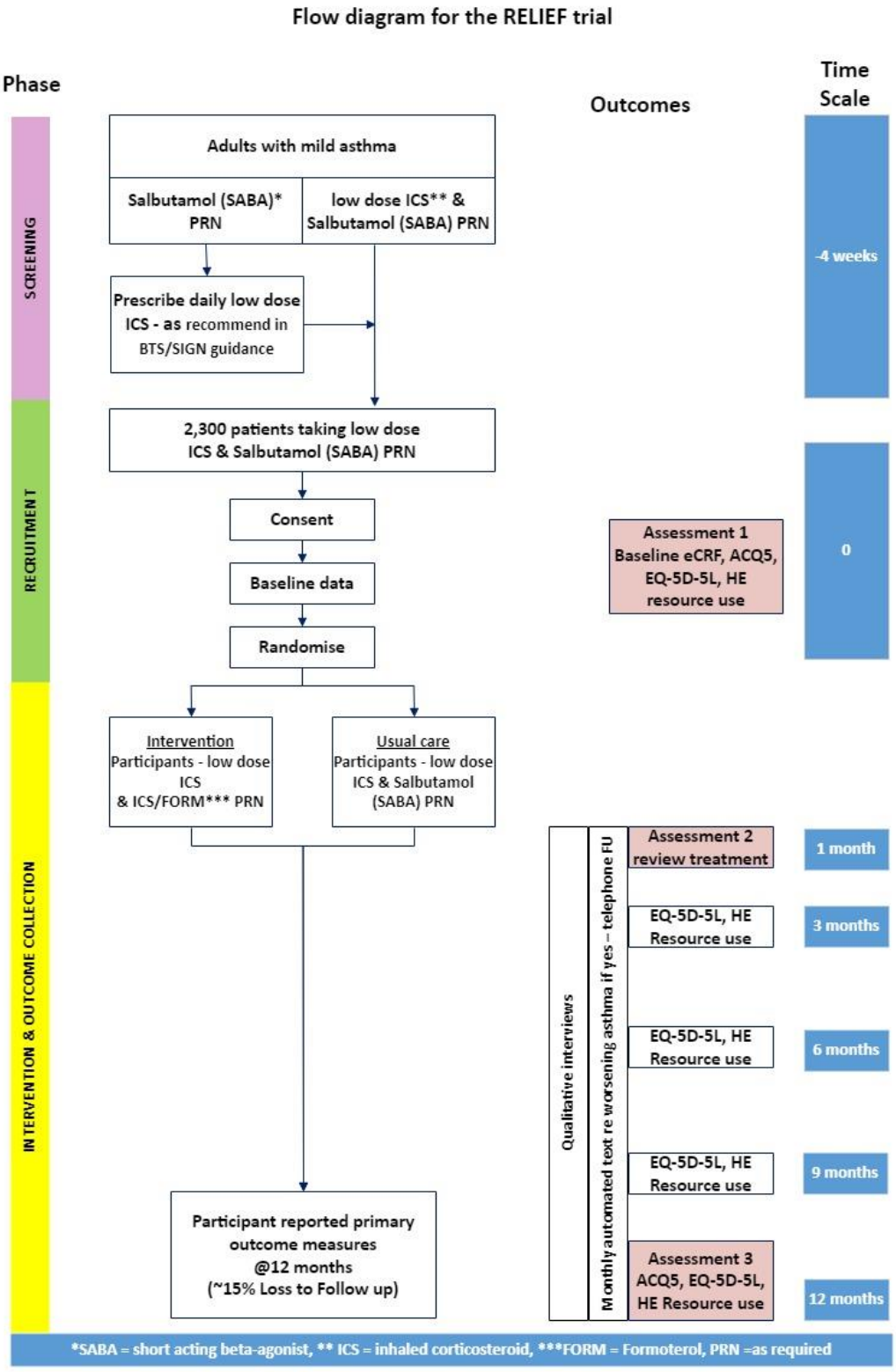
= length of intervention

= time span for variable data collection

***Please note that eConsent completion and site countersignature will be gained prior to the remote baseline appointment taking place.**

If a participant is not able to attend the follow-up visits in person, then data will be collected remotely, via telephone or video consultation, in line with existing NHS procedures for remote clinics. If participants do not attend via other methods then data will be collected from medical records subject to informed consent

Figure 2: Flow diagram for the Relief trial pathway



STATISTICS and DATA MANAGEMENT PLAN

DATA MANAGEMENT PLAN

General

Details about data handling will be specified in the Data Management Plan (DMP). This will include the agreed validation specification which will validate data for consistency and integrity as it is entered.

Data Capture and Data Queries

All trial data will be entered onto a trial specific database through the eCRF with participants identified only by their unique trial number and initials. The database will be developed, maintained and locally hosted by NCTU.

Clinical data will be entered via trial staff at the relevant GP centre via a password restricted mechanism. Patient-reported data will primarily be entered online, also by individual site login details. Those patients who are unable or unwilling to complete data in this manner will be sent questionnaires in the post for return to NCTU via self-addressed envelope.

Description of Data Entry Validation

The database used for the purposes of this trial will be Redcap®**.** Access to the database will be restricted and secure. Any missing or ambiguous data will be queried with the site via the eCRF. Sites should respond to the data queries in a timely manner, ideally within 2 weeks of the query being raised. All access and data transactions will be logged in a full audit trail.

Data Cleaning and Database Lock

Participant's eCRF data will be reviewed and soft locked on an ongoing basis once they are deemed to have a complete set of data that has passed data validation checks (i.e. there are no data queries outstanding). Once all participant data have been soft locked and the statistical analysis plan has been finalised, the trial database will be hard locked (set to read only). This will be done prior to the data analysis. It is planned that database hard lock will occur after the final 12 month follow up.

Monitoring

Central monitoring will be carried out on regular (at least monthly) basis, following a risk assessment, and as documented in the RELIEF Trial Monitoring Plan. Onsite monitoring will be conducted on a triggered basis following discussion of metrics defined in the Monitoring Plan at the TMG. NCTU will be in regular contact with each site's research team to check on progress and address any queries that they may have. The trial team will check incoming eCRF data for adherence with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Additional monitoring (including on-site visits) may be triggered, for example by poor CRF return, poor data quality, lower/higher than expected SAE reporting rates, excessive number of participant

withdrawals or deviations. If an on-site monitoring visit is required, NCTU will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow NCTU trial/monitoring staff access to source documents as requested. Sites will be requested to provide copies of signed ICFs and other documentation for in-house review for central monitoring for all participants. This will be detailed in the monitoring plan.

STATISTICS

Methods

Trial analysis and reporting will be in accordance with CONSORT guidelines. Full details of the planned analyses will be documented in the Statistical Analysis Plan (SAP), which will be agreed with the Trial Steering Committee and finalised before database lock. The statisticians involved in producing the SAP will be blinded to treatment allocation.

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. Baseline demographic and clinical measures will be presented using appropriate descriptive statistics by allocated group.

The primary outcome will be analysed using a Cox proportional hazards regression model adjusted for minimisation variables to estimate a hazard ratio and 95% confidence interval for the between group comparison. Kaplan Meier curves will be presented for time to first severe asthma exacerbation by allocated group. Secondary outcomes will be analysed using appropriate regression models, depending on the type of variable, adjusting for minimisation variables.

Research staff will check medical records at 12-months; therefore, 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 12 months in the primary analysis if participants withdraw consent for access to their GP record or are lost to follow-up and have moved to a different GP practice. Consideration will be given to sensitivity analyses making different assumptions to investigate the potential impact of these participants on the between group estimate.

Subgroup analyses according to smoking status and whether the participant ever had an asthma exacerbation, that required 3 or more days of oral steroids, will be performed by including appropriate interaction terms in the analysis model for the primary outcome. The trial is not powered to detect any interactions hence the subgroup analyses will be treated as exploratory.

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 [21]), 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 [14]. 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 [22]. 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 [11-14]. 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.

Qualitative study analysis

Qualitative data will be analysed using an inductive thematic approach in line with the Braun and Clark methodology. [27]

Assessment of safety

The treatments mandated in this protocol are well established treatments for asthma, with a fully known safety profile. The trial will comply with regulatory requirements by collecting SAEs accordingly, via a combination of SAE forms for expedited reporting and standard CRFs for expected events. In particular, the number of severe asthma exacerbations, hospital admissions for asthma and emergency department attendances are outcomes for the trial. In addition, adverse events and serious adverse events (described in Safety endpoints) will be summarised descriptively according to allocated group.

Procedures for missing, unused, and spurious data

It is anticipated that missing baseline and follow-up data will be minimal. Trial assessments have been limited to baseline, 1 month (remote) and end of trial (remote optional) with the primary outcome recorded from responses to monthly text messages with a medical note review at the end of the trial to check for missing events. The primary outcome will be collected

through a combination of participant reports and checking medical records at 12 months and so should be available for nearly all randomised participants. If the proportion of participants with censored data is higher than expected, consideration will be given to sensitivity analyses making different assumptions to investigate the potential impact of missing data.

Handling of missing data for the secondary outcomes measures will be specified in the statistical analysis plan (SAP).

Definition of populations analysed

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

HEALTH ECONOMICS

Aim

An economic evaluation alongside the trial will be conducted to determine whether the RELIEF intervention is cost effective compared to usual care alone at twelve months post-randomisation.

Methods

The primary economic analysis will be conducted from an NHS and Personal Social Service (PSS) perspective as per NICE guidance (2022). Secondary analysis will take a societal perspective to capture the broader effects of asthma, such as time lost from paid employment, out-of-pocket expenses and potential effect on carers and families. This will enable a broader societal perspective to be reported alongside a health service perspective.

Resource Use

Data from a purposively designed patient resource proforma will collect patient-level resource information using patient self-completion. This measure will collect data on all aspects of patient treatment and follow-up, including medication, primary care visits, secondary care visits - inpatient and outpatient hospital visits, community care and medications related to asthma care and its complications and any out-of-pocket expenses. Within the secondary analysis, data collection methods will be designed to quantify the effect of time off work for patients/carers (including friends and family) and the implications for productivity.

The health economics questionnaire measure will be designed with input from the trial patient advisory group and seek to capture all relevant resource drivers yet minimise patient burden. The purposively designed health economic resource proforma (to be lodged in the UK health economists DiRUM database) will ensure the key resource implications for mild asthma are captured. The proforma will be used to collect data at baseline, 3, 6, 9 and 12 months from all participants. Where data is collected remotely, reminders, including but not limited to, phone calls, emails and text messages will be implemented to maximise retention. Costs will be applied to the resources using data from sources such as the BNF, NHS reference costs and the Unit Costs of Social Care (PSSRU Kent).

Outcome Measurement

Quality of life (QoL) data (EQ-5D-5L) will be collected at baseline, 3, 6, 9 and 12 months to ensure sufficient time points are collected to plot the effects on QoL and health resource use, of this intervention and as such the policy implications compared to usual care.

It is envisaged that a measure of effectiveness in terms of exacerbations will be possible to enable both a CUA and a CEA analysis to occur. The effect of exacerbations in patients will be addressed by examining the association between long-term outcome and costs in the population who experience an exacerbation. Whether exacerbation is an important cost driver in this patient group and the trial and likely implications for their long-term QoL will be examined. The effects on costs and quality of life in the trial arms incorporating any effects of exacerbations will form part of the core analysis of costs and quality of life in the trial arms.

Analysis

The cost data will be combined with outcome data from both clinical measures and the EQ-5D-5L, to enable cost effectiveness and cost utility analyses to be undertaken. The range of costs in the intervention and usual care arms will be examined in a sensitivity analysis. The outcome measure for the economic evaluation will be the number of Quality-of-Life Years (QALYs) based on a 12-month time horizon with no discounting for costs or outcomes as they accrue within a 12-month period.

An intention-to-treat (ITT) incremental analysis will be used between the two groups based on a within trial time horizon. The economic evaluation will be a within trial cost-utility analysis which will estimate the incremental cost per quality adjusted life year gained (QALYs) of the RELIEF intervention compared to usual care alone, at 12 months follow-up. The main outcome measure will be the QALYs derived from the EQ-5D-5L questionnaire completed at baseline, 3, 6 months, and 12 months. These will be combined with patient self-reported NHS and societal costs to inform the cost utility analysis from an NHS perspective and a separate secondary analysis taking a societal perspective. The intention is to do a further CEA using the exacerbations using the same approach as within the CUA analysis.

No discounting will be applied to derived QALYs or costs due to their being incurred within a twelve-month period.

If possible, an incremental analysis will be used between the two groups. Where appropriate, an Incremental Cost Effectiveness Ratio (ICER) will be reported. The net monetary benefit framework will be used, and a net benefit regression implemented to estimate the extent to which, and the probability that, Salbutamol or ICS/formoterol represents the most cost-effective intervention. Cost Effectiveness Acceptability Curves (CEACs) showing the probability of effectiveness versus willingness to pay at the NICE threshold of 20-30k per QALY will be constructed. Key cost drivers will be examined using probabilistic sensitivity analysis.

Modelling

The health economic analysis will further undertake construction of a Markov based health economic lifetime model to determine the effects of the treatment options beyond the one-year

time horizon. Economic modelling is a resource intensive option, but the usefulness of such an approach would lie in the better prediction of costs and outcomes to inform policy makers in the long-term treatment of asthma – a condition affecting a large population over the course of their life.

Study within a Trial (SWAT)

Rationale

It is known that there are several areas of the UK where overuse of SABA and asthma exacerbation rates are particularly high. Many of these contain communities with relatively high numbers of economically disadvantaged people and minority ethnic groups who we know are underrepresented in asthma research. Research suggests ethnicity and migration have both substantial and independent effects on the incidence of asthma [30]. Moreover, it is documented that there are much poorer asthma outcomes in UK among South Asian and Afro-Caribbean communities. This is particularly the case among children of migrants who are seen to be at increased risk of developing asthma when compared to UK-born Whites [30]. Similarly, a more recent article [31] reports poorer incidence of asthma control and increased exacerbation rates among those from the most deprived areas. The magnitude of socioeconomic disparities is also shown to be higher among older patients and those from ethnic minority groups [30, 31]. Understanding the driver of this disparity requires further exploration. In order to address this, the current study has been designed to increase recruitment of participants from these underrepresented groups.

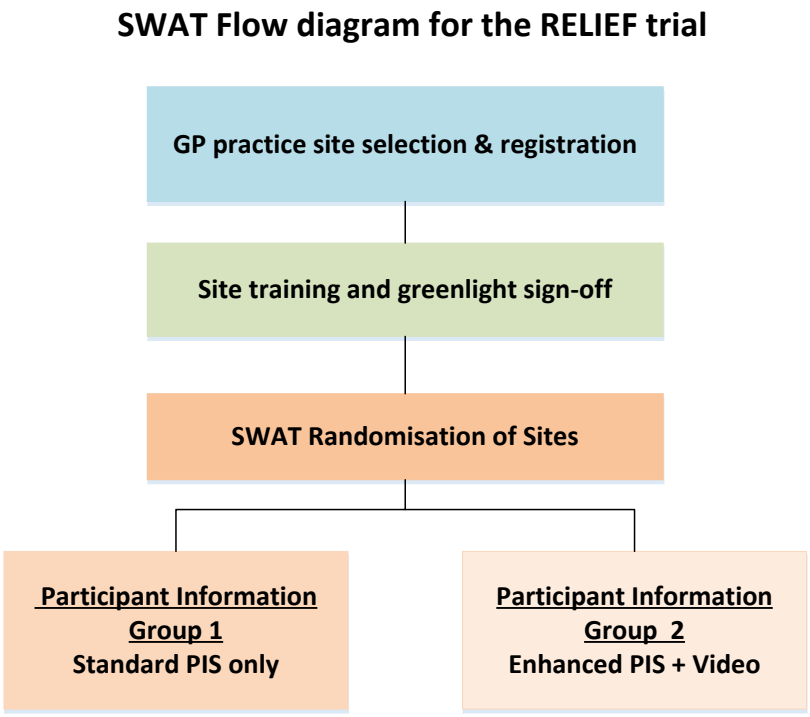
Therefore, alongside the main trial we have further included a SWAT to determine whether an animated video in 4 key languages as well as English improves recruitment. The SWAT is a cluster randomised trial which will investigate the effects of this intervention to improve both overall recruitment and inclusivity in the trial. We have worked with colleagues and PPI groups at the Centre for Ethnic Health Research at Leicester University to create an animated video about the trial that will be dubbed into 4 key languages (Bengali, Urdu, Gujarati and Polish) as well as in English.

The intervention may improve understanding of all participants, not just those in ethnic minority groups, we will therefore include all participants rather than the sub-set from ethnic communities in the SWAT.

SWAT Population: GP practices participating in the RELIEF trial. We intend to specifically target areas with high levels of SABA overuse and asthma exacerbations that often correspond to communities with relatively high numbers of economically disadvantaged people and ethnic minorities. We have incorporated many of the recommendations from the toolkit from the Centre of Ethnic Health Research.

SWAT randomisation: The unit of allocation in the SWAT will be the general practice. GP practices will be randomised 1:1 to intervention or control (figure 3) and balanced according to practice size, percentage of patients in the practice of white ethnicity and deprivation.

SWAT Intervention: Access to an animated video explaining the main clinical trial will be sent via a link to potential participants in addition to use of an enhanced PIS with reply slip to indicate interest in participating in the trial.



SWAT Comparator: Standard PIS alone

Figure 3: SWAT flow diagram

SWAT outcome measures

(1) Recruitment rates in the control and intervention groups of the SWAT;
(2) Proportion of randomised participants who are from ethnic minorities;
(3) Proportion of randomised participants providing follow-up data at 12 months.

SWAT analysis

One interim analysis is planned 18 months after the start of the trial (after 8 months of recruitment). At this point, we predict 38 practices will have been open for at least 3 months and 996 participants will have been randomised. If there was strong evidence of an effect on recruitment rates of either control or intervention, the strategy showing the greatest consent rate would then be implemented for all future patients invited to the trial. Otherwise, the SWAT will continue until the end of the trial.

Interim and final analyses will include appropriate descriptive statistics and between-group comparisons will use appropriate regression models with analysis at the cluster level for recruitment outcomes and participant level for other outcomes using mixed effect models to take account of clustering by GP site.

ADVERSE EVENTS

An adverse event is any unfavourable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the trial.
An AE does include a / an:

1. Exacerbation of a pre-existing illness.

2. Increase in frequency or intensity of a pre-existing episodic event or condition.

3. Condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the trial.

4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

The intervention being evaluated in this trial are treatments that are widely available within the NHS and used in standard care for moderate to severe asthma. However, this trial is using the intervention among those with *mild asthma* which is outside of its licenced usage. Given the low-risk nature of this trial, we will adopt a targeted approach to AE and SAE reporting. We will exclude all adverse events and exacerbations due to disease progression from expedited reporting but will include all serious adverse events related to treatments in the annual development safety update report (DSUR). Targeted incidents as specified in this protocol (e.g. asthma exacerbations), will be documented in the participants medical notes and the trial CRF.

Reporting and follow-up of these targeted participant and investigator-reported complications associated with the intervention delivery will be recorded in trial CRFs in a structured format and do not need to be reported to the Research Ethics Committee (REC).

An AE does not include a/an:

1. Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that led to the procedure is an AE.

2. Pre-existing disease or conditions present or detected at the start of the trial that did not worsen.

3. Situations where an untoward medical occurrence has not occurred (e.g. hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. Disease or disorder being studied, or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. Overdose of concurrent medication without any signs or symptoms.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the IMP or placebo that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event
3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Where any AE event results in an admission to hospital or prolongation of a hospital stay this will also require reporting on a SAE form by the PI or delegate (see section on SAE reporting).

All adverse events will be assessed for seriousness, expectedness, and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals, or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

An AE whose causal relationship to the trial IMP is assessed by the Chief Investigator as “possible”, “probable”, or “definite” is an Adverse Drug Reaction.

With regard to the criteria above, medical, and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Targeted adverse events will be recorded by the research site and monitored until resolution, stabilisation, or until it has been shown that the trial medication or treatment is not the cause.

In the RELIEF trial these targeted AEs are:

- Palpitations
- Pneumonia
- Oral thrush

Sites should report these events via the RELIEF AE Log on becoming aware of them.

Reporting of Serious Adverse Events

Research sites will be asked to contact NCTU immediately upon becoming aware of any serious adverse event. The PI must assess causality of the IMP for any SAE. The Chief Investigator (delegated responsibility by the Sponsor) shall be informed immediately (within 24 hours) of any serious adverse events and shall review causality and assess expectedness in conjunction with any treating medical practitioners.

Notification of pregnancy

If a pregnancy occurs in a participant who is in either arm of the trial, they will be withdrawn from the trial and should follow the direction of their GP. Due to the change in treatment and the low risk associated with the trial medications no trial related adverse events in the mother or child are expected in this trial. However, all serious adverse events will be recorded and reported to the MHRA and REC as part of the annual DSUR. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Sponsor shall ultimately be responsible for adverse event reporting.

Urgent Safety Measures

An Urgent Safety Measure procedure will be initiated if any research participant is identified as being at risk of harm in relation to their involvement in a research project. Urgent action, which deviates from the approved protocol, is required to manage the event, and protect the participant. If any urgent safety measures are taken the CI shall immediately and, in any event, no later than 3 days from the date the measures are taken, give verbal and written notice to the MHRA, the relevant REC and the sponsor, of the measures taken and the circumstances giving rise to those measures. The sponsor must then follow-up with notification in writing within three days of the action being taken. The notification should be in the form of a substantial amendment and should describe the event, the measures taken and justification for the measures taken.

SUSARs

A serious adverse event that is either sudden in its onset (e.g. anaphylaxis), unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall, or are suspected to fall, within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness, and relatedness to the trial IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- If the event is deemed a SUSAR, shall, within seven days, enter the required data on the MHRA's web site.
- Shall inform the REC using the reporting form found on the Health Research Authority web page within 7 days of knowledge of the event
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the trial protocol and inform the ethics and regulatory authorities as required

Trial Treatment Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment but not the IMPs shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness, and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment shall inform the REC using the reporting form found on the Health Research Authority web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.

- Make any amendments as required to the trial protocol and inform the REC as required

Participant removal from the trial due to adverse events

Any participant who experiences an adverse event may be withdrawn from the trial at the discretion of the Investigator. However, this is not a requirement and ideally the site would continue to collect as much of planned data as possible.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), via the combined ways of working review process, the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible, and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health UK Policy Framework for Health and Social Care, 2017.

No ethical or regulatory issues are anticipated. The IMP being evaluated is a licensed product already used "as-required" in moderate-to-severe asthma in the UK and has an excellent safety record. ICS/formoterol as required for symptom relief is also recommended in the latest version of the GINA statement.

The trial has been classed as a type B CTIMP by the Sponsor, and therefore requires a CTA, as well as NHS REC and HRA approval. Further approvals from the Primary Care CRNs for the GP practices within their region will be obtained and greenlight individual GP practices once the requisite paperwork and training are in place.

The trial will be run in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004, together with its amendments; the UK Policy Framework for Health and Social Care Research 2017; GDPR, Data Protection Act 2018 and the University of Nottingham NCTU Quality Management system.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant written or electronic informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that may apply. The investigator or their nominee and the participant shall both sign and date the electronic Consent Form (eConsent via Redcap), or a paper consent Form before the person can participate in the trial. A traditional informed consent form will also be available on request.

The participant will receive a copy of the signed and dated consent form and the original will be retained in the Trial Master file. A third copy will be filed in the participant's medical notes, both scanned and/or stored electronically, or on paper as appropriate. A signed and dated note will be made in the medical notes that informed consent was obtained for the trial.

The decision regarding participation in the trial is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding trial participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the trial, and will discuss with them, whether they wish to continue with the trial. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the trial, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by MHRA and the REC and use of the amended form (including for ongoing participants).

RECORDS

Drug accountability

There are no trial-specific drug accountability requirements; sites and/or local pharmacies will follow their own local procedures for recording treatments dispensed.

(Electronic) Case Report Forms

Each participant will be assigned a unique trial identification number allocated at enrolment, for use on eCRFs, other trial documents and the electronic database. The documents and database will also use this unique trial identification number and the participants' initials (of first and last names separated by a hyphen or a middle name initial when available). Participant contact details will be logged and kept on a partitioned part of the trial database, to ensure participant data is not identifiable.

Participant contact details may also be used by the trial team in order to send out trial related questionnaires, text messages via Esendex, correspondence and follow-ups, limited to the duration of the participant's participation in the trial. Participants may also optionally consent to their contact details being retained beyond the duration of their participation in the trial, in order to be updated about the outcomes of the research or informed of future research. The

database will have in-built validation to ensure that the identifiers used all match with the allocated participant ID number.

CRFs/eCRFs will be treated as confidential documents and held securely in accordance with regulations. CRFs/(e)CRFs will be restricted to those personnel approved by the Chief or local PI and recorded on the Trial Delegation Log. Errors on any paper CRFs will be corrected using standard GCP correction methods (errors will be struck through, initialled, and dated).

The Chief or local PI (or their designee) will sign a declaration ensuring accuracy of data recorded in the CRF /(e)CRF. The CRF/(e)CRF will only collect the minimum required information for the purposes of the trial. Any paper CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities. Electronic data including the trial database will be held securely and password protected.

The PI will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required. CRFs/eCRF shall be restricted to those personnel approved by the Chief or local PI and recorded on the 'Trial Delegation Log.'

CRFs are used to record clinical trial data and are an integral part of the trial and subsequent reports. The CRFs, therefore, must be legible and complete.

All paper forms (if applicable) where possible, shall be completed using black ink. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local PI shall sign a declaration ensuring accuracy of data recorded in the paper CRF.

Source documents

Source documents shall be filed at the investigator's site and may include, but are not limited to, consent forms, current medical records. A CRF/eCRF may also completely serve as its own source data. A source data location log for the trial will outline the different sources of data and their locations. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF/eCRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee, and inspection by relevant regulatory authorities (MHRA).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will

only collect the minimum required information for the purposes of the trial. CRFs will be held securely within the trial database or where in paper format, a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above).

Computer held data including the trial database will be held securely on University of Nottingham servers and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method). Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48, and the clinical negligence scheme for general practice (CNSGP). There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

TRIAL CONDUCT

Trial conduct will be subject to audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting and drug accountability,

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial team at NCTU, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs/eCRFs may be verified by inspection or audit against the source data. In addition, the subsequent capture of the data on the trial database will be checked. Where corrections are required, these will carry a full audit trail and justification.

Trial data and evidence of monitoring and audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local PI will maintain all records and documents regarding the conduct of the trial. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the trial records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archiving facilities. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this trial are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the trial that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments, and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The results will be widely disseminated via national conferences high impact journals, key stakeholders, NHS decision makers and national asthma guidelines. We will inform participants of the trial results and create a video on the trial website explaining the trial results in lay-terms. No participant identifiable information will be reported during dissemination of the results.

The dissemination of the proposed research findings will also be disseminated via a published HTA monograph, research papers for publication in peer reviewed journals, presentation at scientific conferences, and communication of the findings to groups involved in guideline

development. Manuscripts will be prepared by the CI, deputy CI and TMG and authorship will be determined by mutual agreement. Both the TSC and DMC will be given the opportunity to comment on the manuscripts prior to any submission.

Secondary publications and presentations that are prepared by Investigators must be reviewed by the CI, deputy CI and NCTU. Manuscripts must be submitted to either party in a timely fashion and in advance of being submitted for publication, this to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Nottingham.

All publications will acknowledge the support of the NIHR in regard to the funding of this trial.

Trial participants will be asked whether or not they would like to receive a summary of the research findings, following the publication of the results. The research summaries will also be provided to the PPI partners, who can circulate to their membership. Publications arising from further research conducted using shared trial datasets should appropriately acknowledge the trial investigators and funder.
Anonymised participant data may be shared with researchers external to the trial research team in accordance with the NCTU's data sharing procedure. All requests for data should be sent to the Nottingham Clinical Trials Unit.

USER AND PUBLIC INVOLVEMENT

Patient and Public Involvement (PPI) is incorporated in this project throughout the research process and will adhere to the UK Standards for Public Involvement. The Nottingham Asthma Centre (NAC) PPI group were involved from the beginning of this project, identifying the prevention of asthma exacerbations and deaths as a research priority.

A public co-applicant has been included in the project who had input into the trial design and the development of the grant proposal, and they are a member of the Trial Management Group. An independent patient representative will also sit on the Trial Steering Committee.
There will be continuing involvement from the NAC group, throughout the research process and there will be input from the PPI groups within the centre for ethnic health research at Leicester University and from Asthma UK. The impact of PPI within the project will be evaluated by utilising the Public Involvement Impact Assessment Framework (PIIAF) and reported in accordance with the GRIPP2 checklist.

TRIAL FINANCES

Funding source

This study is funded by the NIHR Health Technology Assessment Programme (NIHR131440). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Participant stipends and payments

Participants will not be paid to participate in the trial; however, they will be offered a one-off inconvenience voucher of £15 for attending the baseline appointment whether randomised or not, and reimbursed for reasonable travel costs if applicable.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name) Matthew Martin

Signature: M J Martin
Matthew Martin (May 6, 2025 18:54 GMT+1)

Date: 06/05/2025

Trial Statistician: (name) Yuanfei Su

Signature: Yuanfei Su

Date: 07/05/2025

REFERENCES

1. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach, 2007.
2. Data from Price D (Co-applicant). Optimum Patient Care.
3. Royal College of Physicians. Why asthma still kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry report. London: RCP, 2014.
4. Bourdin A, Bjermer L, Brightling C et al. ERS/EAACI statement on severe exacerbations in asthma in adults: facts, priorities and key research questions. European Respiratory Journal 2019 54: 1900900; DOI: 10.1183/13993003.00900-2019
5. https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/
6. Billington CK, Penn RB, Hall IP. β2 Agonists. Handb Exp Pharmacol. 2017;237:23-40. doi: 10.1007/164_2016_64. PMID: 27878470; PMCID:
7. Bårnes CB and Ulrik CS.Asthma and Adherence to Inhaled Corticosteroids: Current Status and Future Perspective. Respiratory Care March 2015, 60 (3) 455-468; DOI:https://doi.org/10.4187/respcare.03200
8. Suissa S, Ernst P, Francois J et al. A cohort analysis of excess mortality in asthma and the use of inhaled β-agonists. Am J Respir Crit Care Med 1994;149:604–10
9. Suissa S, Ernst P, Benayoun S et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000;343:332–6
10. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginasthma.org
11. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 2018; 378:1865-76.
12. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, Jorup C, et al. As-needed budesonide- formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018;378:1877-87.
13. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, Harrison T, Houghton C, Oldfield K, Papi A, Pavord ID, Williams M, Weatherall M. Controlled trial of Budesonide-formoterol as needed for mild asthma. NEJM 2019;380(21)
14. Hardy J, Baggott C, Fingleton J 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. Lancet 2019;394:919-928
15. Martin MJ, Wilson E, Gerrard-Tarpey W, Meakin G, Hearson G, McKeever TM, Shaw DE, Harrison TW. The utility of exhaled nitric oxide in patients with suspected asthma. Thorax Published online first: February 22nd 2016. doi: 10.1136/thoraxjnl2015-20801
16. Aaron SD, Vandemheen KL, FitzGerald JM, et al. Reevaluation of diagnosis in adultswith physician-diagnosed asthma. JAMA 2017; 317: 269–279
17. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005;99(5):553-558
18. EuroQol: a new facility for the measurement of health related quality of life. Health Policy 1990; 16: 199–208
19. Reddel HK, Taylor DR, Bateman ED et al. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and

Exacerbations. Standardizing Enpoints for Clinical Asthma trials and Clinical Practice. Am J Resp Crit Care Med 2009;180:59-99
20. Fuhlbrigge A, Peden D, Boushey HA et al. Asthma Outcomes: Exacerbations. J Allergy Clin Immunol. 2012;129(3 Suppl):S34-S48
21. McKeever T, Mortimer K, Wilson A, Walker S, Brightling C, Skeggs A, Pavord I, Price D, Duley L, Thomas M, Bradshaw L, Higgins B, Haydock R, Mitchell EJ, Devereux G and Harrison T. Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations. NEJM 2018: 378(10) 902-910.
22. https://www.nice.org.uk/guidance/ng80/evidence/chronic-asthma-management-pdf7079863934
23. Goeman DP, Thien FCKT, Abramson MJ et al Patients' views of the burden of asthma: a qualitative study. The Medical Journal of Australia. 16th September. https://doi.or/10.5694/j1326-5377.2002.tb044786.x
24. Doward L, Svedsater H, Whalley D et al. A descriptive follow-up interview study assessing patient-centred outcomes: Salford Lung Study in Asthma (SLS Asthma). npjPrimary Care Respiratory Medicine 2019;29:31 https://doi.org/10.1038/s41533-019-0142-x
25. Cardet JC, Busse PJ, Carroll JK et al Adherence to adding inhaled corticosteroids to rescue therapy in a pragmatic trial with adults with asthma: A pilot study. Annals of allergy, Asthma and Immunology, 2020:124 (issue 5):487493
26. Akindele, A., Daines, L., Cavers, D. et al. Qualitative study of practices and challenges when making a diagnosis of asthma in primary care. npj Prim. Care Respir. Med. 29, 27 (2019). https://doi.org/10.1038/s41533-019-0140-z
27. Braun, V., & Clarke, V. (2012). Thematic analysis. In H. Cooper, P. M. Camic, D. L. Long, A. T. Panter, D. Rindskopf, & K. J. Sher (Eds.), APA handbooks in psychology®. APA handbook of research methods in psychology, Vol. 2. Research designs: Quantitative, qualitative, neuropsychological, and biological (p. 57–71). American Psychological Association. https://doi.org/10.1037/13620-004
28. Devereux G, Cotton S, Fielding S, et al. Low-dose oral theophylline combined with inhaled corticosteroids for people with chronic obstructive pulmonary disease and high risk of exacerbations: a RCT. Health Technol Assess. 2019;23(37):1-146. doi:10.3310/hta23370
29. Patel R, Naqvi SA, Griffiths C, et al., Systemic adverse effects from inhaled corticosteroid use in asthma: a systematic review, BMJ Open Respiratory Research 2020;7:e000756. doi: 10.1136/bmjresp-2020-000756
30. Netuveli, G. Hurwitz, B. Sheikh, A. 2005. Ethnic variations in incidence of asthma episodes in England & Wales: national study of 502,482 patients in primary care. Respiratory Research. Accessed at https://respiratory-research.biomedcentral.com/articles/10.1186/1465-9921-6-120, accessed 19/05/2022
31. Busby J, Price D, Al-Lehebi R, Bosnic-Anticevich S, van Boven JFM, Emmanuel B, FitzGerald JM, Gaga M, Hansen S, Hew M, Iwanaga T, Larenas Linnemann D, Mahboub B, Mitchell P, Morrone D, Pham J, Porsbjerg C, Roche N, Wang E, Eleangovan N, Heaney LG. Impact of Socioeconomic Status on Adult Patients with Asthma: A Population-Based Cohort Study from UK Primary Care. J Asthma Allergy. 2021;14:1375-1388 https://doi.org/10.2147/JAA.S326213
32. Risk-adapted approaches to the management of clinical trials of investigational medicinal products. 10th October 2011.