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A new relief inhaler for mild asthma

Submission date 24/09/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 13/02/2023	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 27/09/2024	**Condition category** Respiratory	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
About 10% of UK adults have asthma. Many have “mild” asthma, requiring reliever (blue) inhalers for symptoms with or without low-dose-inhaled steroid preventer (brown) treatment. Asthma causes airway inflammation, so treatment with regular inhaled steroids is important. Blue inhalers provide symptom relief but do not help with inflammation. Increasing reliever inhaler use and decreasing the use of preventer inhalers are associated with poorer asthma outcomes. This trial aims to replace the first-choice standard blue inhaler for all asthma patients, recommending instead a combination inhaler containing both a reliever and a preventer medication. Patients get preventer medication every time they use their reliever reducing the problem of low preventer use, providing more when asthma control is getting worse. Combination inhalers used for symptom relief are better than blue inhalers at preventing poor outcomes in patients with moderate/severe asthma. This approach has also shown benefits in "mild" asthma, but more evidence is required. This study will compare “standard care” treatment for “mild asthma” versus “new combined inhaler” + inhaled steroid treatment.
The study aims to determine:
1. The effectiveness of a combination inhaler versus standard care for symptom relief in mild asthma
2. The overall costs and savings of the two approaches
3. Healthcare providers' and patients' perspectives of the new approach

Who can participate?
Patients aged 18 years and over with mild asthma prescribed low-dose inhaled steroids from primary care centres across the UK, with particular focus on areas where blue inhaler overuse and asthma attacks are higher.

What does the study involve?
Patients will be allocated either combination inhaled steroid/formoterol or salbutamol when required for asthma symptom relief. Patients continue to use low-dose inhaled steroids. The main measure to be compared between the two treatments will be the time to the first asthma attack after starting treatment. Patients will be in the study for 12 months, completing questionnaires about asthma and health resource use at several time points. A proportion will also be interviewed.

What are the possible benefits and risks of participating?
This study is comparing two standards of care that are already widely in use across the UK for asthma. The combined inhaler (intervention arm) is routinely used in the treatment of moderate /severe asthma with minimal risks involved. The use of a combined inhaler for symptom relief in "mild" asthma is not yet licenced in the UK. However, the researchers do not expect there to be any additional risks or disadvantages to taking part in the study. The researchers do not know if taking part in the study will directly benefit participants but they hope that the information obtained from this study will help them to understand more about the best way to treat mild asthma. The researchers also hope that the participants gain a better understanding of their asthma and how to control it, and that by being in the study they may be able to avoid having more severe asthma attacks.

Where is the study run from?
Nottingham Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
April 2022 to November 2025

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1006098

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
22040, IRAS 1006098, CPMS 54357

Study information

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

Acronym
RELIEF

Study objectives

Replacing the standard short-acting beta agonist (SABA) reliever inhaler containing salbutamol with an inhaler that contains both the long-acting beta agonist (LABA) formoterol and inhaled corticosteroid (ICS), in patients with mild asthma treated with low dose maintenance ICS, will increase the time to the first severe exacerbation (defined as treatment requiring 3 or more days of steroid tablets).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 19/12/2022, HSC Research Ethics Committee B (Office for Research Ethics Committees Northern Ireland [ORECNI], Business Services Organisation, Unit 4, Lissue Industrial Estate West, Rathdown Walk, Moira Road, Lisburn, BT28 2RF, Ireland; +353 (0)28 95 361404; orec.reception@hscni.net), ref: 22/NI/0151

Study design
Open randomized controlled parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
GP practice

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Mild asthma

Interventions
The trial is comparing a combined ICS/formoterol inhaler against the standard short-acting beta agonist (SABA) inhaler for symptom relief in patients with mild asthma taking low-dose inhaled corticosteroids (ICS). Trial participants will be participating in the trial for 12 months from randomisation to final follow-up.

Group A: Intervention arm
Participants will be randomised to an “as required” combination ICS/formoterol 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), considered to be a nIMP (non-investigational medicinal product) in this trial.

Group B:
Participants will be randomised to an “as required” short-acting beta agonist (SABA) in the form of salbutamol sulfate (comparator). Each dose of salbutamol contains 100micrograms of salbutamol sulfate per 1metered 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.

Exemplar nIMP: All participants will be prescribed an inhaled corticosteroid (ICS) in the form of beclometasone dipropionate which is a 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.

Participants and healthcare professionals cannot be blinded to the treatment allocation due to the nature of the interventions.

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:

1. GP practice
2. Asthma exacerbation requiring at least 3 days of systemic steroids in the last 12 months
3. Treatment with low-dose ICS initiated by the GP in the last month versus ICS treatment started more than 1 month previously

The exact choice of ICS/formoterol or salbutamol will be left to the GP's discretion. The IMPs described above are indicative of the treatment options available, however, a generic equivalent may be prescribed.

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.

Blinding of participants and health professionals is not possible in this trial. Due to the unblinded nature of the trial no emergency unblinding processes are necessary.

Assessments

Baseline

Informed consent will be obtained, when participants attend a baseline appointment - (visit 1) during which the following will be collected:
1. Concomitant medication checks and relevant medical history taken
2. Baseline data including demographic information

3. Asthma Control Questionnaire 5 (ACQ5)
4. EQ-5D-5L
5. Health economic resource use questionnaire
6. Patient's employment and income status

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.

Follow-up

Week 1: Between days 3 & 7 following consent and randomisation, selected participants will be contacted by the qualitative team for interview.

Month 1: Participants will be seen or contacted by telephone at 1 month (visit 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 starting treatment.

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, with a "YES/NO" reply. A "yes" reply will be followed up with a phone call from a member of the research team to confirm the use of prednisolone (or equivalent), clarification of medication and its origin if not prescribed, the dose, the date of commencement, and the duration of treatment.

Months 3, 6, and 9: Participants will be asked by text/email to complete, either online in response to an email link to a REDCap database, or by hard copy sent in the post (if requested), the EQ-5D-5L and a questionnaire to collect health resource use data for the health economic analysis. At month 6 GP staff will also review the previous 6 months' medical records to retrieve the type and number of all asthma inhalers prescribed.

Month 12: At the 12-month end of trial visit (visit 3), which should ideally be a face-to-face appointment, the ACQ5 and EQ-5D-5L will be completed along with the final health economic resource use questionnaire in a quiet area of the GP clinic 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.

Months 2-12: The number of hospital admissions and/or A&E visits for asthma will also be collected during phone calls if the patient has answered "yes" if they have experienced an asthma attack.

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). The interview will explore patients' 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 Redcap. 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 with a small group of participants 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. Additionally, this will ensure there is a representative sample of participants from traditionally under-represented backgrounds (e.g. ethnic minority participants), the proposed sample size should help 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, the researchers 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 about 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 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.

The researchers have worked extensively with their PPI group to design the qualitative interview schedule. They 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 the researchers 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.

Compliance

All GP practices opened as sites within the trial, will review prescriptions for SABA for the first 6 months from randomisation for those participants randomised to ICS/formoterol. 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.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Salbutamol sulfate, beclometasone dipropionate, formoterol fumerate dihydrate, budesonide, formoterol fumerate

Primary outcome measure
Time to first severe asthma exacerbation, defined as treatment with systemic corticosteroids for an asthma worsening, for at least 3 days

Secondary outcome measures
1. Number of severe asthma exacerbations in the 12-month period post-randomisation measured using monthly follow-up phone calls/texts and GP medical records
2. Number of hospital admissions for asthma in the 12-month period post-randomisation measured using GP medical records
3. Number of emergency department attendances for asthma in the 12-month period post-randomisation measured using GP medical records
4. Total SABA, ICS and ICS/formoterol inhalers prescribed in the 12-month period post-randomisation measured using GP medical records
5. Asthma control measured using Asthma Control Questionnaire – 5 (ACQ-5) at 12 months
6. Health-related quality of life measured using EQ5D-5I at baseline, 3, 6, 9 and 12 months
7. The acceptability of the new treatment assessed via an embedded qualitative study at week 1 and 9/12 months

Overall study start date
01/04/2022

Completion date
30/11/2025

Eligibility

Key inclusion criteria
1. Patients aged 18 years 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 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 a 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.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
2,300

Key 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. Participants who are pregnant or who are intending to become pregnant

Date of first enrolment
01/07/2023

Date of final enrolment
31/12/2024

Locations

Countries of recruitment
United Kingdom

Study participating centre
Not provided at time of registration
United Kingdom
-

Sponsor information

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Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer reviewed scientific journals
2. Conference presentation
3. Publication on website
4. Other

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

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Chief Investigator and Trial Management Group and authorship will be determined by mutual agreement.

Intention to publish date

30/11/2026

Individual participant data (IPD) sharing plan

The datasets analysed during this trial will be available to researchers upon request from the NCTU (ctu@nottingham.ac.uk), a minimum of 12 months after the publication of this paper. Access to the data will be subject to review of a data sharing and use request by a committee including the CI and sponsor and will only be granted upon receipt of a data sharing and use agreement. Any data shared will be de-identified which may impact on the reproducibility of published analyses.

IPD sharing plan summary

Available on request