CLINICAL STUDY PROTOCOL

Full Study Title: **A novel reliever strategy for children with asthma: Children's Anti-inflammatory Reliever study, United Kingdom (CARE-UK)**

Short Study title / Acronym: CARE-UK

Product: Budesonide / formoterol combination inhaler

Development Phase: Phase III

Sponsor: Imperial College, London

Version no: 2.0

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This protocol has regard for the HRA guidance

RESEARCH REFERENCE NUMBERS

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This protocol describes the CARE-UK trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to Investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ADE	Adverse Device Effects
AIR	Anti-Inflammatory Reliever
ASADE	Anticipated Serious Adverse Device Effect
cACT	Childhood Asthma Control Test
CHU9D	Child Health Utility Questionnaire
CI	Chief Investigator
CRF	Case Report Form
CRNs	Clinical Research Networks
CTA	Clinical Trial Authorisation
CYP	Children and Young People
DALYs	Disability Adjusted Life Years
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EMD	Electronic Monitoring Device
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HRA	Health Research Authority
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
ICS	Inhaled Corticosteroids
IMP	Investigational Medicinal Product
IND	Investigational New Drug
ITT	Intention to Treat
LABA	Long-Acting Beta Agonists
MART	Maintenance And Reliever Treatment
MDI	Metered-Dose Inhaler
NIMP	Non- Investigational Medicinal Product
PAAP	Personalised Asthma Action Plan
PICs	Patient Identification Centres

PIS	Patient Information Sheet
miniPAQLQ	mini Paediatric Asthma Quality of Life Questionnaire
OCS	Oral Corticosteroids
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QC	Quality Control
REC	Research Ethics Committee
RCTs	Randomised Controlled Trials
RSI	Reference Safety Information
SABA	Short Acting Bronchodilators
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPCRN	Scottish Primary Care Research Network
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
USADE	Unanticipated Serious Adverse Device Effect

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TRIAL SUMMARY

Title	A novel reliever strategy for children with asthma: Children's Anti-inflammatory Reliever study, United Kingdom
Acronym	CARE-UK
Study Aims	To determine the clinical effectiveness, safety and cost-effectiveness of budesonide-formoterol reliever therapy either alone or as part of maintenance and reliever therapy (MART) compared with SABA, reliever therapy, either used as monotherapy or with the child's usual maintenance treatment (prescribed within licence), in children with asthma aged ≥ 6 to <12 years.
Phase	III
Study Design	A 52-week multi-centre, parallel group, open label, pragmatic, 2-arm randomised controlled trial in children aged ≥ 6 to <12 years with a range of asthma severity
Sample size	1,352 (676 per treatment arm)
Eligibility Criteria	1. Clinician diagnosis of asthma 2. Children aged ≥ 6 to <12 years 3. Washout period of 6 months post previous IMP studies 4. Prescribed asthma medication, (within license) in past 6 months (SABA (salbutamol) with or without ICS or ICS+LABA) 5. Parent or carer able to understand the study requirements and willing to provide informed consent
Exclusion criteria	1. Other chronic airways disease including but not limited to bronchiectasis, cystic fibrosis, sickle cell disease 2. Children prescribed non-salbutamol SABA (e.g. terbutaline) as their reliever 3. Already using ICS-formoterol as a reliever 4. Children on step 5, very high dose treatment (e.g. high dose ICS/LABA, prescription of biological therapy such as omalizumab) 5. Any known or suspected contraindications to the medications prescribed in the study or their respective excipients
Treatment / Main Study Procedures	Intervention arm: Budesonide-formoterol two actuations 100/3µg via MDI and spacer as-needed for symptom relief either used alone or in combination with budesonide-formoterol 100/3µg maintenance treatment Control arm: SABA (2 puffs as needed via MDI and spacer) as a comparator reliever either used as monotherapy or with the child's usual maintenance treatment (prescribed within licence)
Interventional IMP	Budesonide-formoterol 100/3µg via MDI and spacer/ Symbicort
Comparator IMPs	SABA, ICS, ICS-LABA used within license

Study endpoints	**Primary endpoint:** The rate of severe asthma attacks per patient per year, defined as worsening symptoms leading to an urgent medical review resulting in the prescription of systemic corticosteroids **Secondary endpoints:** *Clinical effectiveness* 1. The rate of total asthma attacks per patient per year, defined as worsening symptoms leading to an urgent medical review whether or not systemic corticosteroids are prescribed 2. Time to first severe attack 3. Proportion of participants with at least one severe attack 4. Days lost from school due to asthma per year 5. Parent days lost from work for childcare due to asthma per year 6. Change in childhood Asthma Control Test (cACT over the duration of the study 7. Change in miniPaediatric Asthma Quality of Life Questionnaire (miniPAQLQ) over the duration of the study *Safety* 1. Growth during study period (change in height from baseline to study completion at 52 weeks) *2.* Total budesonide-formoterol dose as measured by electronic monitoring device or prescription records at 52 weeks *3.* Total systemic corticosteroid dose prescribed over 52 weeks *4.* Salivary Cortisol testing at baseline visit and final visit for those children prescribed moderate or high dose ICS (Step 3 and 4) *Cost-effectiveness* 1. Change in Child Health Utility (CHU9D) over the course of the study 2. Quality adjusted life years (QALYs) calculated as the area under CHU9D curve 3. Cost of asthma-related health care over 52 weeks
Recruitment	18 months
Treatment duration	52 weeks
Follow up (post trial)	Nil

1. BACKGROUND

Clinical setting: the problem to be addressed

Despite effective therapy and evidence-based guidelines (1-3) children and young people (CYP) with asthma of all severities continue to have poor control and frequent attacks. The United Kingdom (UK) has among the highest rates of CYP deaths associated with asthma in Europe. Asthma attacks are the among the most common reason for hospital admission in CYP (5, 6). There is inconsistent care and outcomes across the UK and those from the most disadvantaged socio-economic groups are 50% more likely to attend the Emergency Department (7, 8). Globally, asthma is one of the leading causes of disease burden in children aged 5-14 years (9) and impact on Disability Adjusted Life Years (DALYs) is among the highest in children (10). Asthma attacks are associated with increased risk of future attacks and asthma death (11, 12) and less favourable evolution of lung function (13, 14).

Asthma was initially considered a disease of bronchoconstriction and hence early treatments were directed at bronchodilatation. The importance of asthma as an inflammatory condition led to the development of inhaled corticosteroids (ICS) in the 1970s. Almost fifty years later, short acting bronchodilators (SABA) continue to be the most frequently used medication for asthma. However, repeatedly, studies have shown that both underuse of ICS, and over-reliance on SABA are common causal themes in severe asthma attacks and death, in both adults and CYP (12, 15, 16). Many paediatricians and primary care physicians are unaware of the dangers of SABAs (17) and CYP adherence to ICS is poor even among those with severe asthma (18). Therefore, there is an urgent need to change our approach to asthma management away from SABA monotherapy over-use and towards better adherence with ICS. This change requires strategies that are safe, effective and which fit with patient behaviour and preferences.

SABA overuse (≥3 cannisters, 600 doses, per year) is common among those on SABA monotherapy as well as those prescribed maintenance ICS (15, 19, 20). This is despite safety concerns regarding SABA therapy including:

- lack of activity against the underlying anti-inflammatory processes in asthma (21, 22)
- potential to increase bronchial hyper-responsiveness and attenuate viral responses thereby increasing asthma severity (23-25)
- establishing a pattern of overreliance on SABAs, leading to entrenched behaviour of as-needed inhaler use (26, 27)
- overuse during an attack leading to delay in seeking medical review, thereby increasing mortality risk (28, 29)

Similar safety concerns have been raised about long-acting beta agonists (LABA) and these concerns have been addressed by LABA always being delivered in combination with ICS (30). Combination ICS-LABA inhalers have traditionally been used as step-up treatment for patients whose asthma remains poorly controlled with ICS alone.

There are a number of LABAs which differ in their onset and duration of action. Formoterol is a fast-acting LABA with a similar onset of action to SABA but longer lasting effect. This rapid onset of action compared to other LABAs, like salmeterol, means that it can be used for immediate relief of symptoms. The concept of ICS-formoterol as a reliever inhaler is not a new one and a large number of studies in adolescents ≥12 years and adults (reviewed below) have assessed the use of ICS-formoterol as both maintenance and reliever treatment (MART). More recently, attention has turned to using ICS-formoterol as required only (anti-inflammatory reliever (AIR) alone), without any maintenance treatment. The evidence for the effectiveness of MART and AIR alone has led to fundamental changes in asthma

management for adults and adolescents. Since 2019, GINA (Global Initiative for Asthma) no longer recommend SABA only treatment for adults and adolescents ≥12 years, and instead ICS-formoterol is the preferred reliever at all treatment steps (31, 32). However, to date there has only been one published study in 4 – 11 year olds of ICS-formoterol MART and no studies in this age group of AIR alone.

The concepts of AIR and MART have been summarised in the GINA executive summary(31):

- Anti-inflammatory reliever (AIR) alone: combination ICS-formoterol taken as needed for symptom relief, without maintenance therapy.
- Maintenance and reliever therapy (MART): daily maintenance ICS-formoterol plus ICS-formoterol taken as needed for symptom relief.

Clinical studies combination inhaled corticosteroid and formoterol

Maintenance and reliever therapy (MART)

A recent systematic review included data from over 20,000 participants ≥12 years enrolled in 17 phase III randomised controlled trials (33). The meta-analysis indicated that for reducing the risk for severe attacks, low to medium dose MART was (i) as effective as regular high dose ICS with as needed SABA (ii) more effective than lower doses of ICS or fixed combination ICS/LABA with SABA as a reliever. A meta-analysis of 1847 adolescents enrolled in 6 MART RCTs demonstrated significant reductions in the risk of severe attacks and time to first attack favouring MART(34).

There is only one study of MART in 341 younger children aged 4-11 years (35). This study was carried out over 15 years ago and sponsored by the manufacturer. This was a three-arm study comparing very low dose budesonide/formoterol MART (80/4.5mcg once daily maintenance plus additional doses for symptom relief); fixed combination (80/4.5mcg once daily with SABA reliever); and fixed high dose budesonide (320mcg BUD once daily with SABA reliever). There was a reduction in severe attacks by 70 - 79% compared to fixed high dose ICS and fixed combination respectively. This study was carried out in children with moderate asthma. No studies have been carried out in children with mild asthma.

Anti-inflammatory reliever (AIR) alone

Two recent systematic reviews and meta-analysis of AIR alone have been published (36, 37). The Cochrane review included data from studies that compared AIR alone with SABA monotherapy or regular ICS plus SABA as required (36). Six studies were included of which five contributed data to the meta-analysis. All studies used budesonide-formoterol. A total of 9657 participants were included with a mean age of 36 to 43 years. Two studies included adolescents (≥12 years). Compared to SABA alone, ICS-formoterol reduced asthma attacks requiring oral corticosteroids (OCS) (OR, 95% CI 0.34-0.60). Compared to regular ICS there was no difference in rate of asthma attacks. Changes in asthma control, spirometry and quality of life favoured regular ICS over AIR alone however these were small differences which were less than the minimum clinically important difference.

The second systematic review compared AIR-alone (all used ICS-formoterol) with regular ICS plus SABA reliever (37). Four studies with 8065 participants were included. AIR alone was associated with significantly increased time to first severe attack, reduced rate of severe attacks and reduced daily ICS dose.

The studies carried out to date have differed in their design. Two studies were randomised double blind placebo control trials (SYGMA I and II) (38, 39). Although an ‘as needed’

strategy was being tested all participants took regular inhalers (placebo or ICS) in addition to reliever medication. Two other studies (NOVEL START and PRACTICAL), both of which only recruited adults, were open label studies and therefore more closely resembled the way in which this strategy would be used in clinical practice (40, 41). In the latter two studies the risk of severe attacks was significantly reduced in the AIR alone group compared to regular ICS.

Subgroup analysis of participants aged 12 – 18 years, enrolled in SYGMA I and II, also demonstrated a significant reduction in attacks compared to SABA only treatment, and a similar rate of attacks compared to regular ICS, despite those in the AIR alone group taking a significantly lower overall ICS dose. The effect size was larger in the adolescent population compared to the total study population. Height increased from baseline more rapidly with AIR alone compared to regular ICS treatment, reflecting the lower total ICS dose taken.

Other anti-inflammatory reliever strategies

A number of studies have used an anti-inflammatory reliever strategy (use of ICS whenever SABA is needed: ICS+SABA); two of which have been in children (42, 43). The Treating Children to Prevent Exacerbations of Asthma (TREXA) study reported the safety and efficacy of ICS+SABA therapy as needed in children with moderate asthma (42). This was a double-blind placebo-controlled trial. 288 children aged 6-18 years were randomised to one of four arms: (i) combined arm (maintenance ICS with ICS plus SABA for rescue); (ii) daily arm (maintenance ICS with SABA for rescue); (iii) rescue arm (ICS plus SABA as needed) and (iv) placebo arm (SABA only as needed). All children were given 3 inhalers: 2 rescue inhalers (ICS or placebo plus SABA) and one maintenance inhaler (ICS or placebo). The frequency of attacks was lower in all groups than the placebo arm (SABA only) and treatment failures (defined as a second severe asthma attack or hospital admission) were significantly higher in the SABA only arm compared to the other three arms. Height velocity was significantly reduced in the combined and daily arm compared to the placebo and rescue arm.

The Asthma Symptom-Based Adjustment of Inhaled Steroid Therapy in African-American Children (ASIST) study recruited 206 6–17 year old African American children (43). This was an open label pragmatic equivalence trial. Children were randomised to one of two groups: Intermittent, symptom-based adjustment (as needed low dose beclomethasone taken whenever SABA was used); or provider based, guideline-directed adjustment (regular daily beclomethasone plus as needed SABA with subsequent guideline-based dose adjustments). There was no difference in the primary outcome (change in Asthma Control Test score) or in the number of severe attacks between the two groups, but the dose of ICS used was lower in the intervention group, and the intermittent strategy was preferred by families.

There is an ongoing study in the UK comparing as needed ICS with regular ICS (44). However, all these studies are limited by their use of ICS and SABA as separate inhalers and therefore in clinical practice, it is likely that children would be more likely to use the SABA inhaler only, due to the instant relief of symptoms and either forget or choose not to then use the separate ICS inhaler. There are also logistical implications of carrying two inhalers and knowing which one to use, particularly for younger children.

A SABA-budesonide fixed dose combination rescue inhaler is currently undergoing trials, the first of which was recently published (45). This was a phase III, double blind, randomised controlled trial comparing two strengths of SABA-budesonide as a reliever with SABA only

reliever. The participants had moderate asthma and continued with their usual maintenance therapy. A total of 3,232 patients were randomized, of whom 97% were ≥ 12 years (mean age 49 years). The risk of a severe attack was significantly lower with the high dose SABA-budesonide rescue inhaler compared to SABA only over the 24-week study period. Due to the very small number of children enrolled no subgroup analysis is possible and growth indices could not be assessed, thus limiting the conclusions that can be drawn in the paediatric population.

Risk / Benefit Assessment

Benefits

The use of anti-inflammatory reliever therapy has demonstrated efficacy in adolescent and adult studies; however, this treatment option is currently not available to children due to a lack of clinical trial data. The main benefit of this study will be to provide that data – if concordant with previous studies the benefit to participants will be a reduction in asthma attacks.

An additional benefit will be the use of Clinical Research Networks (CRNs) to enable recruitment of children in primary care with a range of asthma severities. Most Investigator-led paediatric asthma studies focus on children with severe asthma. This study will include a diverse population, involving underserved groups as well.

Risks

The main risk is the excessive use of ICS-formoterol as part of the reliever regime. In order to mitigate this risk we will include measurement of height velocity and measure salivary cortisol at the baseline visit and final visit. We will also use electronic monitors in a sub-group to accurately assess total budesonide-formoterol doses. Excessive use of budesonide-formoterol was not seen in previous adult and adolescent studies; indeed the budesonide-formoterol group participants in the as needed only arms used substantially less ICS. However, it is important to assess in this population.

Clinical data on exposed pregnancies are not available for any of the IMPs. If menarche has been experienced by female participants the study investigators must use their clinical judgment to determine if pregnancy testing is indicated or if additional counselling on contraception is required in line with standard care practices for asthma patients and as detailed in the IMP SmPC.

As this study involves a paradigm shift in the way that asthma is managed there is a risk that participants and caregivers will not understand the concept and logistics of using an anti-inflammatory reliever. The rationale will be carefully explained. All participants will be given a Personal Asthma Action Plan (PAAP) which will clearly state when additional doses should be taken, the maximum number of reliever doses to be taken in a day and when to seek urgent medical attention.

The budesonide-formoterol inhaler expires three months after being taken out of the foil (although the expiry date on the box is usually one year). Participants will be given instructions to swap their reliever inhaler for a new one after three months and will be given sufficient supplies when the IMP is dispensed. There is a risk that they will continue to use the inhaler beyond three months out of foil if there are doses left, this is common in clinical practice. Reminders will be sent to mitigate this risk and at the 4 and 8 month visits (which will be carried out by telephone / video) the study nurse will check again that the inhalers have been swapped. Participants will be asked to return all used and un-used inhalers at

the end of the study so that we can assess how many have been used and check participant adherence.

Safety will be monitored throughout the trial by the Data Monitoring Committee (DMC) and any concerns will be raised with the DMC.

2. IMP LIST AND DEFINITIONS

Designated IMPs used throughout the protocol are as follows:

***Investigational IMP* used in the intervention arm:**

- Budesonide-formoterol/ Symbicort

***Comparator IMP* used in the control arm:**

- SABA reliever, ICS or ICS-LABA (or as listed in Appendix 3, Table 7)

3. OBJECTIVES AND ENDPOINTS

Primary Objective

To determine the clinical effectiveness of budesonide-formoterol reliever therapy either AIR alone or as part of MART compared with a SABA reliever either used as monotherapy or with the child's usual maintenance treatment (prescribed within licence)

in children with asthma aged ≥ 6 to <12 years of age over 52 weeks.

Secondary Objective

To determine the safety and cost-effectiveness of budesonide-formoterol reliever therapy either AIR alone or as part of MART compared with a SABA reliver either used as monotherapy or with the child's usual maintenance treatment (prescribed within licence)

in children with asthma aged ≥ 6 to <12 years of age over 52 weeks.

Primary Endpoint

The rate of severe asthma attacks per patient per year: defined as worsening symptoms leading to an urgent medical review resulting in the prescription of oral systemic corticosteroids.

Secondary Endpoints - *Timepoint of evaluation = 52 weeks*

Clinical effectiveness

1. The rate of total asthma attacks per patient per year, defined as worsening symptoms leading to an urgent medical review whether or not oral systemic corticosteroids are prescribed
2. Time to first severe attack
3. Proportion of participants with at least one severe attack
4. Days lost from school due to asthma per year
5. Days lost from work for childcare due to asthma per year
6. Change in childhood Asthma Control Test (cACT) over the duration of the study

7. Change in miniPaediatric Asthma Quality of Life Questionnaire (miniPAQLQ) over the duration of the study

Safety

1. Growth during study period (change in height from baseline to study completion at 52 weeks)
2. Total budesonide-formoterol dose as measured by electronic monitoring device or prescription records at 52 weeks
3. Total composite systemic corticosteroid dose prescribed over 52 weeks
4. Salivary Cortisol testing at baseline visit and final visit for children prescribed moderate or high dose budesonide-formoterol (step 3 and 4)

Cost-effectiveness

1. Change in Child Health Utility (CHU9D) over the course of the study
2. Quality adjusted life years (QALYs) calculated as the area under CHU9D curve
3. Cost of asthma-related health care over 52 weeks

4. STUDY DESIGN

The study will be performed at selected investigational sites in the United Kingdom. Participants will be randomised to one of two treatment arms as shown in Table 1. budesonide-formoterol will be administered as needed or as part of maintenance and reliever treatment as set out in Table 1. Participants in the control arm will continue with their usual medication (SABA reliever, either alone as needed; or as needed with the child's current maintenance preventer treatment (prescribed within licence)). All participants will be enrolled for 52 weeks.

Design

A 52-week multi-centre, parallel group, open label, pragmatic, 2-arm randomised controlled study.

Treatment regimens

The interventional IMP for the interventional arm of the study is budesonide-formoterol 100/3 MDI. The comparator IMPs for the control arm of the study consists of either SABA reliever, ICS or ICS-LABA (prescribed within license), as set out in Table 4.

Table 1.

Treatment Step	Comparator IMP (Control Arm)	Intervention IMP (Intervention Arm)
Step 1	SABA 2 puffs as needed	Budesonide-formoterol 100/3 3 puffs as needed
Step 2	Low dose ICS twice daily plus SABA 2 puffs as needed	
Step 3	Moderate dose ICS or low dose ICS-LABA twice daily plus SABA 2 puffs as needed	Low dose budesonide-formoterol 100/3 1 puff twice daily plus 2 puffs as needed

Step 4	Moderate dose ICS-LABA or high dose ICS twice daily plus SABA 2 puffs as needed	Moderate dose budesonide-formoterol 100/3 2 puffs twice daily plus 2 puffs as needed

5. TREATMENTS

Treatment arms

Following randomisation participants will be allocated to either the intervention arm or control arm. Those in the intervention arm will be issued with two budesonide-formoterol (Symbicort®) 100/3 MDIs and a compatible spacer device such as Aerochamber Plus. One for home, maintenance and reliever doses, and the other to be kept at school for reliever use.

All children will be shown how to use the inhaler and correct technique will be confirmed by the study nurse. They will be issued with a Personalised Asthma Action Plan (PAAP) detailing the number of maintenance budesonide-formoterol doses to be taken (if applicable), the total number of reliever doses that can be taken on a single occasion, total number of doses that can be taken in a day and when to seek help (based on a traffic light system) (see Table 2).

Children will be advised to take 2 reliever puffs as needed, up to a maximum of 8 on a single occasion. If the amber zone threshold is reached participants are advised to seek medical advice within 24 hours. If the red zone threshold is reached participants are advised to call an ambulance and go to the emergency department immediately.

The reliever dosing is based on the recommended dosing for children using budesonide-formoterol maintenance and reliever treatment in the 2023 GINA strategy document (https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf).

The PAAPs are based on the standard Asthma and Lung UK plans which can be found in Appendix 1.

Table 2.

Reliever: budesonide-formoterol use (Interventional Arm)	Action
Using extra reliver doses most days for one week	See their GP within one week to review or amend their current maintenance therapy
More than 12 total (maintenance and reliever) inhalations a day	Go to the hospital or see their doctor or asthma nurse today
More than 16 total (maintenance and reliever) inhalations a day	They need to attend the emergency department or an urgent care centre immediately

Those in the control arm will continue with their current treatment and will be reminded at each study visit to collect prescriptions.

Correct inhaler technique will be demonstrated and checked by the study nurse. If they do not have a spacer device this will be issued as part of standard of care practices.

They will be issued with the Asthma and Lung UK PAAP detailing maintenance treatment (if applicable) and number of SABA doses that can be taken and when to seek help, based on a traffic light system (Table 3).

This will be the same for all treatment steps:

Salbutamol 100 mcg is approved for use in children with asthma of all ages and is the most common reliever inhaler used for asthma.

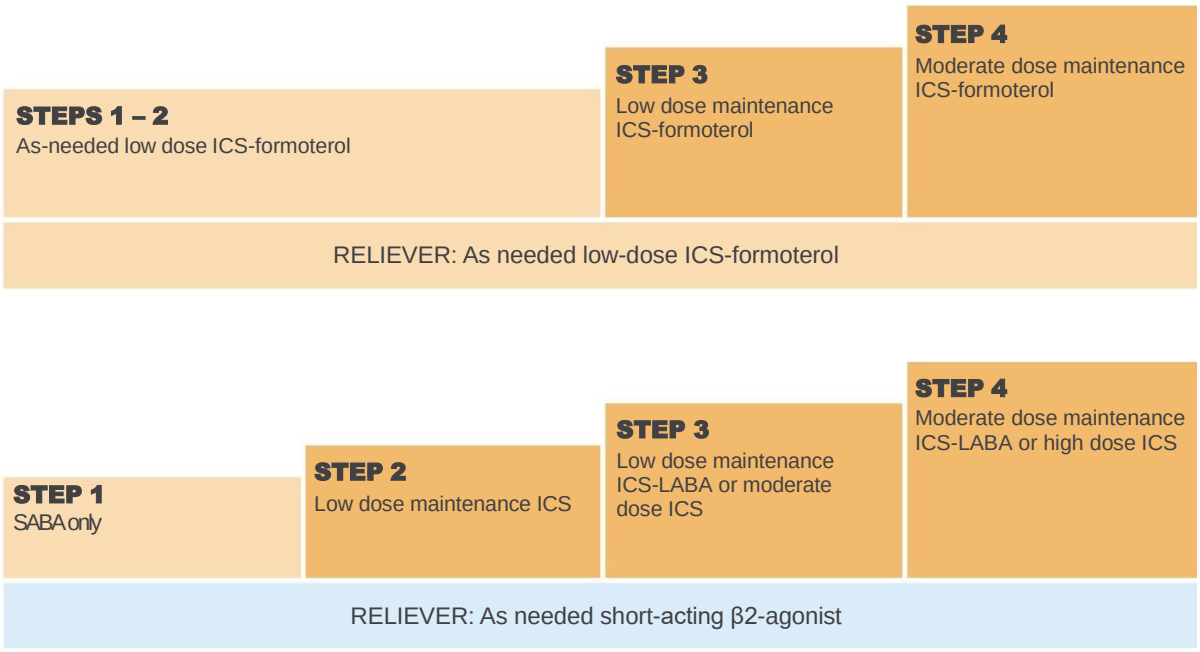
Salbutamol 200 mcg (2 inhalations) and formoterol 6mcg (2 inhalations) achieve a similar bronchodilator response.

The advice below will be provided to participants randomised to the control arm, and is incorporated in their PAAP (provided at Visit 1 and reviewed at all subsequent visits):

Table 3.

Reliever: Comparator IMP use (Control Arm)	Action
Needing reliever inhaler three or more times per week	See their GP within one week to review or amend their current maintenance therapy
More than 6 inhalations every 4 hours	Go to the hospital or see their doctor or asthma nurse today
More than 10 inhalations on a single occasion or reliever inhaler not lasting 4 hours	They need to attend the emergency department or urgent care centre immediately

Figure 1. Overview of study arms



The treatment steps in Figure 1. are derived from the current GINA recommendations. In clinical practice treatment is stepped up and down depending on clinical control in terms of symptoms and risk of an asthma attack. Stepping up and down will be determined by the participant's usual healthcare provider. For those in the intervention arm participants will increase or decrease the number of maintenance budesonide-formoterol puffs per day. The control arm will continue as per usual clinical care whereby the ICS dose is increased or decreased and additional controllers such as LABAs are added or removed depending on clinical control.

The classification of ICS dose (low, moderate, high) and hence the starting step for budesonide-formoterol, will be based on the dose prescribed in the past 4 weeks as per current GINA guidance (Table 4):

Table 4.

	Paediatric low dose	**Paediatric moderate dose**	**Paediatric High dose**
Beclomethasone dipropionate			
Standard particle CFC free inhalers	100 - 200mcg/day	>200 - 400mcg/day	>400 - mcg/day
Extra-fine particle CFC free inhalers	50 - 100mcg/day	>100 - 200mcg/day	>200 - mcg/day
Budesonide			
Metered dose and dry powder inhalers	100 - 200mcg/day	>200 - 400mcg/day	>400 mcg/day

Fluticasone propionate			
Metered dose and dry powder inhalers	100mcg/day	150 – 200mcg/day	>200 mcg/day

6. PARTICIPANT ENTRY

Children will be recruited from primary care (via CRNs) and also from hospitals providing secondary and tertiary care for children with asthma.

Target population

The target population is children aged ≥ 6 to <12 years, with doctor diagnosed asthma, managed either in primary care or in a hospital-based clinic.

(i) Inclusion criteria

1. Doctor diagnosis of asthma
2. Children aged ≥ 6 to <12 years
3. Washout period of 6 months post previous IMP studies
4. Prescribed asthma medication, within licence, in past 6 months (SABA (salbutamol) with or without ICS or ICS+LABA)
5. Parent or caregiver able to understand the study requirements and willing to provide informed consent

(ii) Exclusion criteria

1. Any medical condition which, at the Investigator's discretion, may present a safety risk or impact the feasibility of the study or the study results (including, but not limited to, other significant respiratory comorbidities, such as cystic fibrosis and bronchiectasis)
2. Children prescribed non-salbutamol SABA (e.g. terbutaline) as their reliever
3. Already using budesonide-formoterol as a reliever
4. Children on step 5, very high dose treatment (e.g. high dose ICS-LABA, prescription of biological therapy such as omalizumab)
5. Any known or suspected contraindications to the medications prescribed in the study or their respective excipients

7. PROCEDURES AND MEASUREMENTS

A summary of all the procedures and measurements can be found in Table 5.

7.1 Identification and recruitment of participants

1. **The Clinical Research Network (CRN) and Scottish Primary Care Research Network (SPCRN)** will be used to screen for eligible patients based on coding for

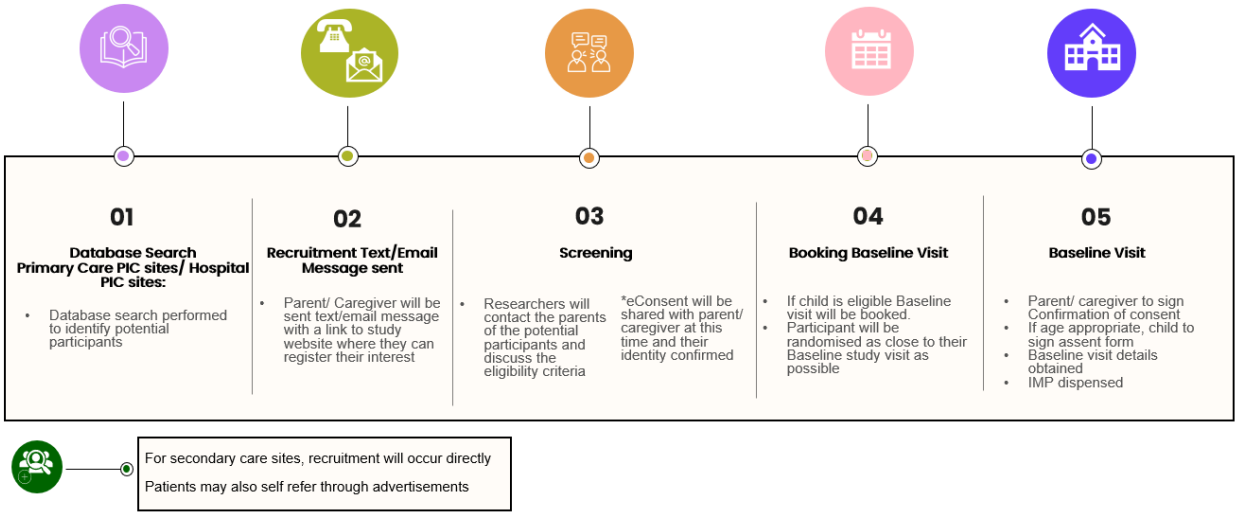
asthma diagnosis and asthma treatment. The CRN will then send an expression of interest to GP practices. The GP practices will act as Participant Identification Centres (PICs) and send either a text message or a one page summary via email as an invitation to view more details about the study including a link to the study website for eligible participants. In Scotland the SPCRN staff will identify eligible cases from GP records and send the study contact details via email. The contact text message or email from CRNs and SPCRNs will include a link or QR code to the study website which will provide a brief study summary and PIS (both parent and child versions) with further information about the study. If parents/ caregivers wish to proceed with the study, they will be asked to answer pre-screening questions on the website which will determine basic eligibility. At this point they will see if their child is potentially eligible for the study. If they would like to continue, the parent/ caregiver will be asked to securely enter their contact details onto the website form and select their local study site where the visits will take place and a member of the study team will be in contact to answer questions and further determine eligibility of the potential participant.

If a potential participant is determined to not be eligible for the study based on the online pre-screening there will be an option for the parent/ caregiver to be contacted by the study site to further discuss why their child may not have been eligible.

2. **Local study sites**: 25 selected asthma centres throughout the UK will also recruit eligible patients attending clinics at the site. Participants will be identified from electronic patient records. Identification of potential eligible children may also occur at other secondary care sites which will act as Patient Identification Centres (PICs) located close to the specialist paediatric centres.
3. We will also accept **self-referrals** direct to the study site (e.g. via universities and other public places using posters, via local newspapers e.g. Metro and Evening Standard, via social media and radio, videos, pop up events and research recruitment websites) which will provide contact details for the study team and links to the study website.

The trial is registered on the National Institute of Health Research (NIHR) Clinical Research Network (CRN) Portfolio, enabling eligibility for National Health Service (NHS) service support costs and interaction with the UK Clinical Research Facilities and the Study Support Service.

Figure 2. Recruitment Flow Chart



7.2 Screening, Informed Consent and pre-randomisation evaluations

All parent/ caregiver details input into the study website form will be allocated to the nearest/ most convenient study site selected by the parent/ caregiver. Once the study site receives this information they will contact the parent/ caregiver to discuss details of the study, answer any queries and ask if they would like their child to participate in the study – this first contact is considered the Screening visit.

7.2.1 Screening visit

The Screening visit will be carried out virtually either over the telephone or via video platform such as NHS Attend Anywhere. The information collected will include the following:

- Informed consent (parent)
- Current medication

Review of inclusion and exclusion criteriaThis study will consist of a two-step consenting process, once virtually, which is considered the primary consent and occurs at the Screening and once in person at the Baseline visit to re-confirm consent, child assent and participant identity.

The study team will explain the study and answer any questions the parent/ caregiver might have. Parents/ caregivers will be given an adequate amount of time to consider their child's participation in the study. If there are no further questions and they decline more time to consider, the parent/ caregiver will be sent a link to the e-consent - upon signature of the e-consent the screening questions can be asked and eligibility determined. This must be completed before any screening activity can begin – signing the e-consent is step one of the two-step consenting process.

Photo ID must also be verified at this stage, this can be done over video call or at the in person visit – parent/ caregiver ID will be verified against the signed e-consent form.

Once the consent form is signed, the study team will review the previously completed *pre*-screening questionnaire (completed by the parent from the study website) and go through the inclusion and exclusion criteria on OpenClinica to formally determine eligibility.

If the child is eligible for the study they will be randomised and invited to come to the research site for the in-person Baseline visit. Consenting and randomising prior to the Baseline visit allows for low risk study activities to proceed whilst Symbicort (the intervention arm IMP) is being dispensed in readiness for the Baseline visit. Preparing Symbicort ahead of the Baseline visit will minimise the time spent at the study centre and inconvenience for the child and their parent/ caregiver.

At the start of the in person Baseline visit the study team will ask the parent/ caregiver to re-confirm their e-consent by signing a paper Confirmation of Consent form, indicating they still want their child to take part in the study. Then, the study team will ask the child if they are happy to take part in the study and if they are, they will be asked to sign the Assent form (if age appropriate). This is the second stage of the consenting process – at this point the study team is able to confirm that the parent and child understands the study and are comfortable taking part.

At the Screening visit, if the parent/ caregiver decides they find it more convenient to sign a paper informed consent they may request this. The parent/ caregiver and their child would then be invited to do an in person Screening visit and then a separate in person Baseline visit – no eligibility or participant randomisation could be determined prior to signing the e-consent.

The patient will be sent a copy of the signed Consent Form. A paper copy of the e-consent will be printed and filed in the relevant section of the ISF and the participant's medical records. The original will be retained in the electronic research record for the patient at sites

Patient Information Sheet

The Patient information Sheet (PIS) will be available on the study website but during the Screening visit this can be sent electronically to the parent/ caregiver in parallel if requested. The child will also have access to their own patient information sheet, with content appropriately adapted for age, on the study website and this can be sent electronically in parallel as well if requested. All participant information sheets are prepared in partnership with Asthma and Lung UK and the patient advisory groups. These will be available in different languages as appropriate and requested.

7.2.2 Randomisation and Blinding

If the child is eligible for the study they will be randomised. A computer-generated randomisation list will be created and allocation concealed using an online system (OpenClinica). Stratified block randomisation will be used. The randomisation will be stratified by:

a. Site
b. Current GINA treatment step, i.e., step 1 and 2, and step 3 and 4 and,

The study is open label. Blinding is not being performed in order to maintain the potential real-world advantage of ICS-formoterol as a reliever.

7.2.3 Baseline and Follow-up visits

Following the Screening visit the Baseline in person visit will be scheduled.

At baseline, data will be collected on medical history including co-morbidities, asthma history, and attack history in the past year. During the Baseline and Final visit, physical examination (chest auscultation), salivary cortisol sample collected (for children in medium to high dose ICS i.e. step 3 and 4), height and vital signs (heart rate) will be measured.

If salivary cortisol levels are found to be low (<12.5nmol/l), the participant will be referred for an adrenocorticotropic hormone (ACTH) stimulation test (short Synacthen test).

After the Baseline visit there will be 3 follow-up visits at 4 monthly intervals (in person at baseline and final visit). Follow up visits 2 and 3 (at month 4 and 8) will be completed via telephone or video platform such as the NHS Attend Anywhere platform. The last follow-up visit (at month 12) will be in person.

For those unable to access the online platform, a face-to-face or telephone visit will be offered.

At each study visit parents and children will be asked details of asthma attacks, adverse events and serious adverse events (hospitalisations), days lost from school due to asthma, and parent/ caregiver days lost from work for childcare due to asthma, changes in asthma medications unscheduled healthcare attendances for asthma over the preceding 4 months.

Additionally, parents will be contacted monthly via text message to collect data on the primary outcome (severe attacks needing a systemic corticosteroids).

The childhood Asthma Control Test (cACT), the miniPaediatric Asthma Quality of Life Questionnaire (miniPAQLQ) and the Child Health Utility questionnaire (CHU9D), along with inhaler checks that will be administered at all study visits via OpenClinica.

Female participants from both arms will be asked if they have experienced menarche at each visit. The study PI must use their clinical judgment to determine if pregnancy testing is indicated or if additional counselling on contraception is required in line with standard care practices for asthma patients and as detailed in the IMPs SmPC.

Participants will be provided with a Personalised Asthma Action Plan at the baseline visit and this will be reviewed at all subsequent visits and re-issued if any changes are made. This will reinforce the randomised treatment regimens including maximum reliever doses and when to seek medical attention. Inhaler technique will be checked at all visits and checks will be made to ensure that the reliever inhaler has been swapped if they have been out of foil for three months or are empty (whichever comes sooner) (46). A review by the child's primary care physician, asthma nurse or paediatrician will be advised if deemed necessary by the study Investigator. Children will continue to be managed by their usual clinician who will determine treatment changes as clinically indicated. The GP letter will provide an algorithm for stepping up and down treatment for the intervention arm. The control arm will have their treatment changed according to current standard clinical care.

Prescription records, detailing total ICS and SABA inhalers in the control arm and courses of OCS for all participants will be obtained for all participants.

The information collected at each study visit is outlined in Figure 3 and the visit schedule (Table 5).

A summary of measurements and assessments at each visit is also outlined below:

Baseline visit (visit 1, in person)

The baseline visit will be carried out face to face at the closest study centre. The information collected will include the following:

- Confirmation of Consent (parent)
- Informed Consent (child, in person) *see Section 7: Screening, Informed Consent and pre-randomisation evaluations
- Demographics
- Asthma history review, including:
    - Age at diagnosis
    - Current and previous medications (last 52 weeks) for asthma
    - Reliever therapy use in the last 4 weeks
    - Current maintenance therapy (ICS or ICS-LABA use in the last 4 weeks)
    - Concomitant medications
    - Total number of courses of systemic corticosteroids in past 52 weeks
    - Unscheduled healthcare visits for asthma (including to primary care, urgent care centres and emergency departments) in the past 52 weeks
    - Hospitalisation for asthma in the last 52 weeks, and any other hospitalisations
    - Current use of a Personalised Asthma Action Plan
    - Childhood Asthma Control Test score (cACT) - this is a validated measure of asthma control
    - Mini Paediatric asthma quality of life questionnaire (miniPAQLQ)
    - Child Health Utility questionnaire (CHU9D) for use in economic evaluation

- Medical history
    - Medical History including coexisting atopic diseases
    - Other medical conditions
    - Exposure to tobacco smoke/ e-cigarettes

- Assessments
    - Physical examination
    - Height (using a stadiometer)
    - Vital signs
    - Determine if menarche has been experienced
    - Collection of Salivary Cortisol sample
    - Electronic monitoring devices issued (see section 8 EMDs)

- Asthma education
    - Inhaler Check
    - PAAP issued

- Intervention IMP (Symbicort 100/3 MDI) Dispensed
    - Inhaler given

Follow up (visit 2 and visit 3, remote)

These visits will be conducted by telephone or video. Information collected will include the following:

- Side effect review
- Determine if menarche has been experienced
- Asthma attacks requiring a course of systemic corticosteroids
- Changes in medication
- Unscheduled healthcare visits for asthma (including to primary care, urgent care centres and emergency departments)
- Hospitalisations due to asthma
- cACT
- miniPAQLQ
- CHU9D
- Days off school (participant) & days off work (parent/ caregiver)
- Adverse events
- Serious adverse events
- Asthma education
    - Inhaler check
- IMP dispensed
- Monthly text message to track any asthma attacks

Final visit (visit 4, in person)

The final visit will be carried out in person at the local study centre. In addition to the information collected at visits 3 and 4 the following will also be collected:

- Physical examination
- Height (using a stadiometer)
- Vital signs
- Collection of Salivary Cortisol sample
- Prescription check of asthma medications prescribed by Primary Care for past 12 months (or duration of study for those who withdraw from the study, provided appropriate consent is obtained to collect this data).
- Collect used and unused inhalers to determine adherence

Between study visits

Between visits participants or their parents/ caregivers will be contacted by text and asked to reply **yes / no** to the following questions:

I. Has your child been prescribed a course of steroids for asthma in the past month?

II. Has your child been admitted to hospital because of asthma in the past month?

III. Has your child had to see their GP, out of hours carer (such as a walk in centre or urgent care centre) or attended an Accident and Emergency Department in the past month because of their asthma?

IV. If the reliever inhaler has been opened for 3 months, have you swapped to a new inhaler? (*Intervention arm only*)

If the answer to any of the questions I to III is “yes” the parents/ caregivers will be contacted by telephone by the study nurse so that additional information can be obtained about the asthma attack. If the reliever inhaler has not been swapped after 3 months of being opened, the study team will contact the parents to remind them to change the inhaler.

7.2.4 Assessment of adherence using electronic monitoring devices – SUBGROUP STUDY ONLY

In order to assess the fidelity of the intervention and for safety purposes, a subgroup (15% in each arm) will be issued with electronic monitoring devices. This will assess adherence to maintenance treatment (both arms) and number of additional reliever doses in the intervention arm and hence total ICS dose in each arm (47). The costs of these devices preclude provision to all study participants. 20 devices will be allocated to each site, thus between 10 and 15 participants will be enrolled in the monitoring subgroup study at each site. Participants will be advised to switch the monitoring device to the new inhaler when the current inhaler has expired or is empty (whichever is sooner). The data from the monitoring device will be downloaded at each study visit. Parents will be asked to sync the device in the app to enable the data to be downloaded remotely for telephone follow up visits. Parents/ caregivers will be shown how to do this.

Figure 3: Trial Flow Chart

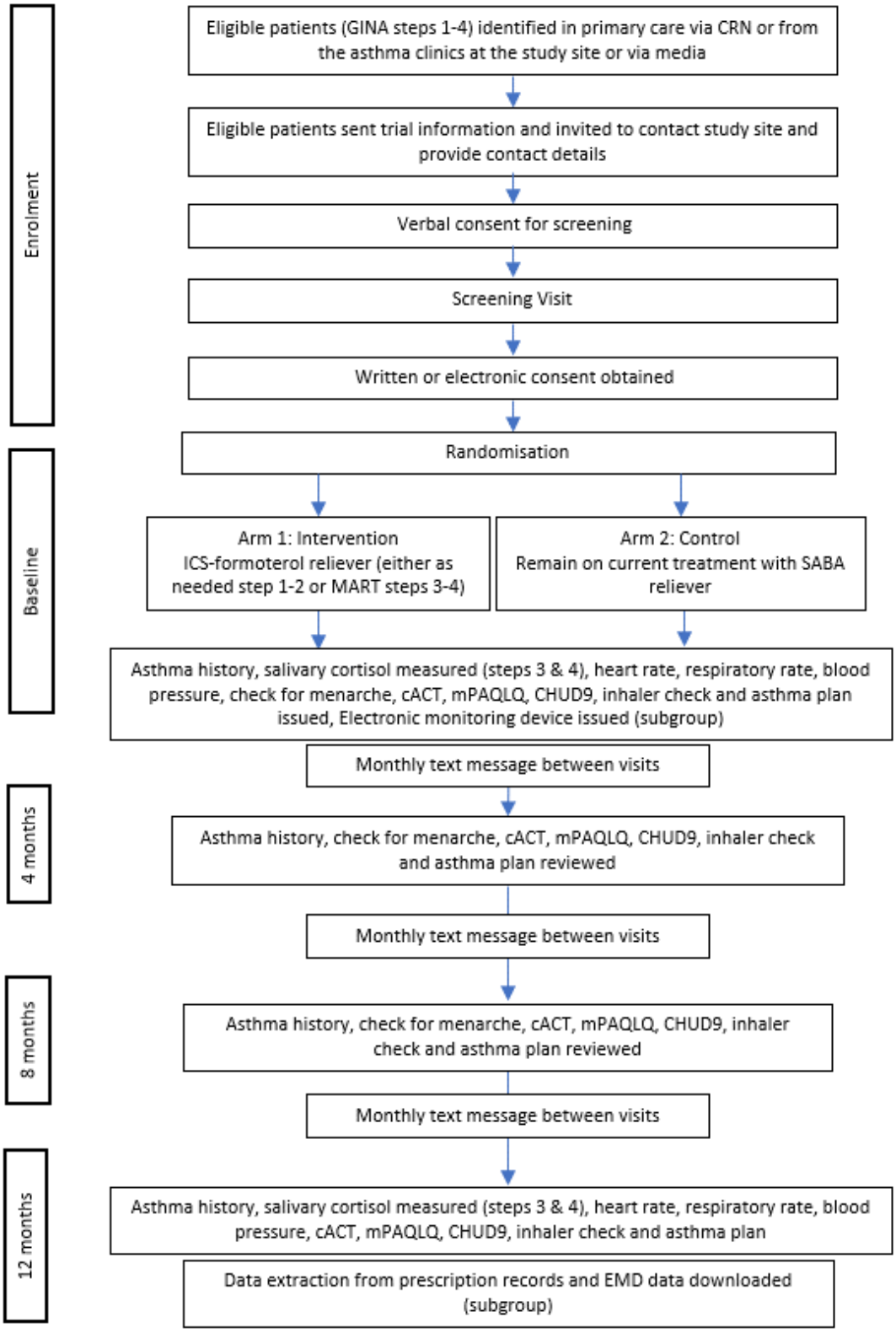


Table 5: Visit Schedule

Visit	Telephone screening	Baseline visit	Follow up visit[1]		Final visit[1]
Visit number	0	1	2	3	4
Time	Day 1	0 – 28 days post Screening visit	16 weeks post Baseline visit	16 weeks post Follow Up visit 2	16 weeks post Follow Up visit 3
Window		min 1d / max 28d (post screening)	min 84d / max 140d (post visit 1)	min 84d / max 140d (post visit 2)	min 84d / max 140d (post visit 3)
Informed consent	X[3]	X[4,5]			
Algorithm for inclusion/exclusion	X				
Randomisation		X (pre visit once consent obtained)			
Adverse events			X	X	X
Demographics		X			
Asthma / attack history		X	X	X	X
Past medical and drug history		X			
Current medications	X	X	X	X	X
Physical Examination		X			X
Height		X			X
Vital signs		X			X
Menarche history[7]	X	X	X	X	
Salivary Cortisol test[6]		X			X
cACT		X	X	X	X
miniPAQLQ		X	X	X	X
CHU9D		X	X	X	X
Personalised Asthma Action Plan		X	X	X	X
Education and Inhaler technique		X	X	X	X
Electronic Monitoring Device issued[2]		X			
Electronic Monitoring Device data downloaded[2]			X	X	X
IMP (ICS-formoterol) dispensed		X	X	X	

1. Monthly text messages between visits
2. Subgroup only
3. Parental informed consent (e-consent)
4. Confirmation of Consent (at Baseline visit in person)
5. Child assent (in person to confirm identity and understanding of study)
6. Children prescribed medium to high dose ICS only (step 3 and 4)
7. Female participants only

Incidental findings

Any incidental findings discovered throughout the study will be referred back to the participant's GP.

8. DESCRIPTION OF PROCEDURES AND MEASUREMENTS

Childhood asthma control test (cACT)

- The cACT is a 7 item questionnaire, with 4 picture cased questions for children and 3 items for parent/ caregivers. Score ranges from 0 – 27 with a score ≥ 20 indicating good control.

miniPaediatric asthma quality of life questionnaire (miniPAQLQ)

- The miniPAQLQ has 23 questions in 3 domains (symptoms, activity limitation and emotional function). Each item is scored on a 7 point scale. The overall miniPAQLQ score in the mean of all 23 responses (ranging from 1 to 7) with lower scores reflecting greater functional impact of asthma.

Child Health Utility Questionnaire (CHU9D)

- The CHU9D is a paediatric generic preference-based measure of health-related quality of life. It consists of a short questionnaire and a set of preference weights using general population values. The questionnaire has 9 questions with 5 response levels per question and is self-completed by the child.

Physical Examination

- Performed by the PI or a designated member of the study team, as part of standard of care practice, this physical examination will include measurement of:
    - Chest auscultation using a stethoscope

Height Measurement (using a Stadiometer)

- Performed by designated study staff, participants will have their height measured using a calibrated stadiometer, in a standardised manner:
    - Shoes must be removed each time (socks or bare feet)
    - Heels must be placed against the measuring backplate

- Child must be standing straight up with head and eyes parallel to the floor (ears over shoulders)
- Height to be measured to the last millimetre

Vital Signs

- Performed by the PI or a designated study nurse, as part of standard of care practice, this vital sign check will include the measurement of:
  - Blood pressure using an appropriate sized cuff designed for children
  - Respiratory rate observe the rise and fall of the chest wall. The number of times the chest wall rises within 60 seconds should be recorded
  - Heart rate using an electronic sphygmomanometers which include automatic recording of heart rate
    - If this is not included the heart rate should be obtained by palpating the radial pulse and measuring the rate for 60 seconds

Menarche

At each study visit menarche history will be checked for female participants. If menarche has been experienced the study investigators must use their clinical judgment to determine if pregnancy testing is indicated or if additional counselling on contraception is required in line with standard care practices for asthma patients and as detailed in the IMP's SmPC.

Collection of Salivary Cortisol Sample

At the Baseline and Final visit, a salivary cortisol sample will be collected from participants prescribed medium or high dose ICS (see Table 2) i.e Step 3 and 4. The passive drool method will be used whereby the child drools either directly into the collection pot or using a straw. These samples are to be labelled, stored and shipped according to the Salivary Cortisol collection guidelines.

Electronic monitoring devices

- A subgroup (15% in each arm) will be issued with electronic monitoring devices to assess adherence to maintenance treatment and number of additional reliever doses in the intervention arm and hence total ICS dose in each arm.

  Each centre will be allocated 20 devices and the first 10-15 participants who enrol at each study site will be issued with a device.

  The data will be downloaded at each study visit. Parents will be asked to sync the device in the app to enable the data to be downloaded remotely for telephone follow up visits. They will be instructed to move the monitoring device to a new inhaler once a new inhaler is taken out of foil and shown how to do this.

Asthma Education/ Inhaler Check

- Asthma Education (including inhaler check) will be performed by a designated study staff who have completed the NHS England e-learning Tier 2 or 3 capability:
    - *Asthma Care for Children and Young People (Tiers 2 or 3).*
- A Personalised Asthma Action Plan will be provided as outlined in section 6 below

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP) DETAILS

The IMP that is being studied in this trial is budesonide-formoterol (Symbicort) metered dose inhaler containing 100 mcg budesonide and 3 mcg formoterol respectively. Symbicort is manufactured by AstraZeneca in accordance with Good Manufacturing Practices. It is currently licenced as a maintenance treatment for asthma or maintenance and reliever treatment for adults and adolescent (12 years and over) with asthma.

Symbicort Turbohalers (containing either 100 mcg or 200 mcg of budesonide plus 6 mcg of formoterol) are licensed from 6 years of age for maintenance treatment. There are concerns about children using Turbohalers (dry powder devices) as a reliever as they may not generate an effective inspiratory flow when acutely breathless. In this age group the reliever (salbutamol) is usually prescribed as an MDI (metered-dose inhaler) to be used with a spacer. By using the Symbicort MDI with Aerochamber Plus spacer device in this age group we are replicating the mode of delivery for the reliever inhaler in both treatment arms.

The reliever dose (as set out in section 6.1) is based on the recommended dosing for children using ICS-formoterol maintenance and reliever treatment in the 2023 GINA strategy document (https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf).

The trial is being carried out under a Clinical Trial Authorisation (CTA). The drug is therefore only to be used by the named Investigators, for the participants specified in this protocol, and within the trial.
The Summary of Product Characteristics (SmPC) for Symbicort 100/3, last updated 24-May-2023 will be used (https://www.medicines.org.uk/emc/product/11855/smpc/print) for the IMP. Sites should refer to their Investigator Site File or ICTU for the current version. The IMP is a marketed product and are manufactured in accordance with GMP standards.

The IMPs in the control arm are SABA relievers, ICS or ICS-LABA (prescribed within license), as set out in Table 7. Currently licensed ICS and ICS+LABA for children (including Clenil Modulite and Seretide), are set out in Appendix 3.
These comparator IMPs will be prescribed and managed by the participant's GP. Please refer to their individual SmPCs.

Labelling and Packaging

A third-party packaging/distribution company, WGK Clinical Services Ltd., will handle all aspects of the interventional IMP studied in this trial. The interventional IMP supply will be labelled at Wasdell Packaging Limited as an IMP and shipped to sites by WGK Clinical Services Ltd.

Storage and Dispensing

Budesonide-formoterol should be stored at room temperature in accordance with the SmPC. The shelf life when packaged is 2 years.

Once opened the shelf life is 3 months. Therefore, at study visit 1 participants will be issued with:

4 inhalers (steps 1 and 2);

5 inhalers (step 3) and;

7 inhalers (step 4)

Two to be opened immediately (one for home use, one to be kept at school) and used for 3 months and then swapped for the unopened inhalers.

For those in Step 3 the maintenance inhalers will last for 2 months (assuming 100% adherence).

For those in Step 4 the maintenance inhalers will last for 1 month (assuming 100% adherence). The dates when the unopened inhalers are due to be opened will be indicated on the label.

If further reliever inhalers are needed the parent/ caregiver will be advised to contact the study team.

Budesonide-formoterol will be prescribed using a study-specific prescription and dispensed by site pharmacy staff for administration during study visits. Following remote visits budesonide-formoterol will be posted out to the participants.

Dosage, Duration and Compliance

Budesonide-formoterol dosing depends on treatment step as set out in section 3 above. The participants in the intervention arm will remain on budesonide-formoterol for the duration of the study. The dose may be stepped up or down as per standard clinical care, in line with the stepwise dosing guidelines.

Participants will be asked to return all empty and un-used inhalers to their study site pharmacy for destruction at the of the study to ensure that inhalers were swapped appropriately and as a measure of adherence/ total usage.

Accountability

Site pharmacies will maintain accountability records for budesonide-formoterol which will be reviewed during site monitoring visits throughout the trial. Any un-used budesonide-formoterol supply will be checked by the study Monitor and destroyed locally following receipt of approval from the Monitor.

Drug interactions / Precautions / Contraindications

Sites should refer to the current approved version of SmPC for budesonide-formoterol for up-to-date information regarding drug interactions, precautions and contraindications.

Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided.

Beta-adrenergic blockers can weaken or inhibit the effect of formoterol.

Budesonide and formoterol have not been observed to interact with any other drugs used in the treatment of asthma.

The only contraindication is hypersensitivity to budesonide or formoterol or to any of the excipients.

Overdose of IMP

The maximum daily dose of budesonide-formoterol 100/3 is 16 puffs. Overdose of formoterol would likely lead to effects typical for β_2 adrenoceptor agonists (including salbutamol): tremor, headache, palpitations. In an adult, the study a dose of 90 mcg (equivalent to 30 inhalations) of formoterol administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression may appear. As a safety measure, height and salivary cortisol will be measured in this study as a measure of hypercorticism and adrenal suppression respectively.

Sites should refer to the SmPC of budesonide-formoterol for the up to date information regarding a potential overdose. If an overdose is suspected, the patient should be monitored for any abnormal signs or symptoms. Medical treatment should be sought and instituted appropriately.

Dose Modifications for Toxicity

There are no recommendations for dose modification of the budesonide-formoterol, doses will be prescribed in accordance with the applicable Summary of Product Characteristics and PAAP provided.

Study drug administration

Symbicort MDI will be used with a spacer with mouthpiece. If children are unable to form a good seal with a mouthpiece they will be advised to use a spacer and mask. Inhaler technique will be shown and checked for all participants.

Pre-medications details

Salbutamol MDI with or without ICS or ICS+LABA (prescribed within license) will be used as the IMP comparator drug using a spacer with mouthpiece within the control arm of the study. If children are unable to form a good seal with a mouthpiece they will be advised to use a spacer and mask. Inhaler technique will be shown and checked for all participants. Medications in the control arm (Comparator IMPs) will be prescribed and managed by the participant's GP.

10. PERMANENT DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL FROM STUDY

(i) Permanent discontinuation of study treatment

Participants may discontinue study treatment for the following reasons:

- At the request of the patient / patient's family
- Adverse Event/ Serious Adverse Event: that have resulted from treatment administration where the Investigator considers that it would not be safe for the patient to continue treatment, e.g. anaphylaxis. A serious adverse event that is not considered clinically related to the drug intervention will not be a criterion for withdrawal.
- Eligibility violation e.g. contraindication of budesonide-formoterol or participating in another trial of an investigational medicinal product
- Allergic reaction to budesonide-formoterol
- If the Investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study.
- Sponsor terminated study
- DMC/ TSC terminated study

In the event that the participant discontinues the study treatment, they will be invited to continue attending their remaining study visits to allow for collection of the remaining study data.

(ii) Withdrawal from Study

Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:

-
- Participant /parent or caregiver's decision
- Loss to follow-up

(iii) Procedures for Withdrawal from Study

If a participant withdraws from the study, they will be invited to attend an in person visit so height and salivary cortisol can be measured and key outcome data collected.

If a participant withdraws from trial procedures, an assessment must be made as to whether trial data collected to date can be retained and analysed for the trial.

The decision to withdraw from further trial procedures will be documented on the electronic case report form (eCRF). If the participant does not agree for data collected to be retained, the data will be excluded from the analyses.

Participants who have discontinued the trial intervention and/ or have withdrawn from the trial will not be replaced, as the sample size allows for potential loss to follow-up.

Co-enrolment

Study participants can be enrolled to other observational studies but not to other CTIMP trials. The study team should be informed about enrolling a study participant to other observational studies.

11. PHARMACOVIGILANCE

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial medication, whether or not considered related to the IMP.

Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting Investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions (ARs). The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information as set out in the Reference Safety Information (RSI) (in the Investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the RSI section of the SmPC/ IB which occur in a more severe form than anticipated are also considered to be unexpected.

Expectedness assessment will be performed by the Sponsor or site PI to assess expectedness.

Causality

The assignment of causality for adverse events should be made by the Investigator responsible for the care of the participant using the definitions below. The expectedness assessment will be performed and confirmed by the Sponsor or person delegated by the Sponsor to assess expectedness.

If any doubt about the causality exists the local Investigator should inform the study coordination centre who will notify the Chief Investigator. The pharmaceutical companies and/ or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the Investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Unrelated: No evidence of any causal relationship

Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Severity of Adverse Events

Mild: Awareness of event but easily tolerated

Moderate: Discomfort enough to cause some interference with usual activity

Severe: Inability to carry out usual activity

Adverse Event recording

For the purposes of the study, all AEs will be recorded and reported from the time of informed consent until the last study visit. For the control group, AEs will be reported according to the class of the medication prescribed. All AEs will be recorded in the patient medical notes and on the eCRF. All SAEs will be recorded and reported from the time of informed consent throughout the study via eCRF until the last study visit.

All such AEs, whether expected or not, should be recorded in the adverse event section of the case record form within one month of the form being due.

The trial physician will decide what the best course of action is i.e. referral to GP, hospital, clinic or other. AEs will be followed up according to local practice until stabilised, resolved, diagnosed/ treated or the last trial follow-up visit, whichever is sooner.

Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that:

- Results in death
- Is life-threatening*
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

* "Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

(i) AEs/SAEs excluded from safety reporting

Asthma exacerbations will be recorded and reported from the time of informed consent until the last study visit and they will be analysed as study-specific endpoints on the appropriate form within the eCRF where appropriate.

(ii) Adverse Events of Special Interest (AESI)

The following adverse events of special interest have been defined for this trial, these will be captured on specific forms on the eCRF:

- Infections and infestations:
    - Candida infections in the oropharynx
    - Pneumonia
- Respiratory, thoracic and mediastinal disorders:
    - Mild irritation in the throat, coughing, dysphonia including hoarseness

(iii) Reporting of SAEs

Rapid reporting of all SAEs i.e. within 24 hours, occurring during the study must be performed as detailed in the study-specific safety reporting instructions.

Active monitoring of participants after the end of the trial is not required but if the Investigator becomes aware of safety information that appears to be drug related, involving a participant who participated in the study, even after an individual participant has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF). Copies of completed/updated SAE reports will be sent to the Sponsor throughout the trial. The SAE form asks for the nature of the event, date of onset, severity, corrective therapies given, outcome, expectedness and causality.

(iv) Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the participant.

(v) Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Reference Safety Information (RSI) section 4.8 of the Summary of Product Characteristics (SmPC) for Symbicort.

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(vi) Reporting of SUSARs

SUSARs should be notified to the appropriate regulatory authority, the relevant REC and the Sponsor in accordance with regulatory requirements. SUSARs which are fatal or life-threatening will be reported not later than seven days after alerting the sponsor to the reaction. Any additional relevant information will be sent within eight days of the report.

A SUSAR which is not fatal or life-threatening will be reported within 15 days of first knowledge by the sponsor.

Follow up of participants who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

Developmental Safety Update Reports / Annual Safety Reports

Developmental Safety Update Reports (DSUR) / Annual Safety reports will be submitted to the Sponsor, the Ethics Committee and Regulatory Authority in accordance with local / national regulatory requirements.

Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

12. STATISTICAL ANALYSES

Sample Size and power considerations

The sample size has been calculated based on the anticipated rate of severe attacks in usual care and the estimated risk reduction based on preliminary data.

Children with milder asthma (step 1 and 2 therapy) and more severe asthma (step 3 and 4 therapy) will be recruited and randomisation will be stratified by site and severity. The anticipated rates of attacks in each of these strata is 15 and 40 per 100 per year as determined from existing literature and the expected proportion of more severe asthma is 40%, for a combined total attack rate of 25 per 100 per year (35, 42, 43).

One study of beclomethasone-formoterol compared to SABA as reliever in adults taking maintenance beclomethasone-formoterol reported a reduction in attack risk of 36% with beclomethasone-formoterol (48). Reported relative rates for combined budesonide-formoterol reliever therapy compared with SABA only reliever therapy across the spectrum of asthma severity in adults are between 0.7 and 0.4 (29, 40, 49). In the one study of MART in children aged 6 to 11, the reduction in the risk of severe attacks with budesonide-formoterol MART vs maintenance budesonide-formoterol plus SABA was 0.25 (35). In a systematic review and meta-analysis of RCTs investigating budesonide-formoterol MART vs comparator treatments incorporating a SABA reliever, the relative risk of first severe attacks with MART was at least as great in adolescents as in adults [0.49 (0.34-0.70) vs 0.65 (0.50-0.72)] (34).

Based on these data, a conservative relative rate of 0.65 is proposed, that would correspond to a reduction of the attack rate from 25 to 16 per 100 per year. 575 per arm (total 1150) will give 90% power with two-sided alpha of 0.05 to detect this treatment effect, and including a 15% drop out rate, a total number of participants of 1,352 is needed.

Planned recruitment rate

The study will take place across 25 Clinical Research Networks in the UK. It is estimated that an average of 2-3 patients will be recruited at each centre per month, giving a total of 1352 children recruited to the study over 18 months.

Internal pilot

An internal pilot will take place during the first 6 months after recruitment has started. It will use a traffic light system.

Red = discuss with the Trial Steering Committee (TSC) stopping the trial;

Amber = employ mitigation strategies in discussion with TSC;

Green = continue as planned.

The primary pilot metrics will be reported as point estimates alongside 95% CIs, and assessed against the pre-specified traffic light progression criteria:

- Site set up (number open to recruitment/ number required for full study recruitment):
  - 80% green, 60 - 80% amber, 60% red
- Recruitment rate (number recruited per open site per month/ anticipated open site recruitment per month):

- >70% green, 40 - 70% amber, <40% red
- Retention rate in study (number consented/ number retained to 12 weeks):
  - 80% green,
  - 70 - 80% amber,
  - 70% red (this will be monitored throughout by the Data Monitoring Committee (DMC)

Table 6.

Progression criteria	Red	Amber	Green
Trial recruitment	<40%	40 – 70&	>70%
Recruitment rate/site/month	1	1 - 2	2 - 3
Number of sites opened	14	15 - 19	20 - 25
Total number of participants recruited at month 6	84	90 - 228	240 - 450
Retention rate in study	59	63 - 182	>192

Statistical analysis

Statistical analysis:

Statistical analysis will be by intention-to-treat (ITT). The primary analysis is by estimation of the relative rate of total attacks per participant per year by Poisson regression, with an offset for the time of observation and fixed effects of randomised treatment allocation and randomisation stratification factors. A secondary sensitivity analysis will include the following potentially important predictors of response: age, sex, ethnicity, baseline cACT score, and the number of severe attacks in the previous year, to account for different distributions of these variables in the treatment groups and to increase precision of the estimates of differences. Survival analysis with Kaplan-Meier plots and Cox's proportional hazards will be used to calculate the hazard ratio for time to first severe attack or any attack. Height, miniPAQLQ and cACT scores will also be analysed by ANCOVA with the baseline measurement, randomised treatment and stratification factors as explanatory variables. All statistical tests will be two-tailed with a 5% significance level. A detailed description of all the analyses will be given in the statistical analysis plan (SAP).

13. REGULATORY, ETHICAL AND LEGAL ISSUES

Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the 7th revision of the 1964 Declaration of Helsinki.

Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

Research Ethics Committee (REC) Approval

(i) Initial Approval

Prior to the shipment of the Investigational IMP (Symbicort 100/3 MDI) and the enrolment of participants, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet and Consent Form, any other written information that will be provided to the participants, any advertisements that will be used and details of any participant compensation.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

The trial team, in collaboration with the Sponsor will assess whether a proposed amendment is substantial or non-substantial. For each proposed amendment, a revised version of the protocol will be prepared using tracked changes, a new version number assigned and the revised document will be reviewed and approved by Protocol Development Group and Sponsor prior to submission to the REC and Health Research Authority (HRA). The amended protocol will be sent to participating sites for local approval to be granted and the approved version will be shared with all staff involved in the trial.

(iii) End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines.

The end of trial notification will be submitted within 90 days of the end of trial definition being met. In the event of a premature halt of the trial, the timeframe is 15 days, and the reasons should be clearly explained in the notification.

Regulatory Authority Approval

Clinical Trial Authorisation from the MHRA must be obtained prior to the start of the study. In addition, the MHRA must approve amendments prior to their implementation (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

This study has sought Clinical Trials Authorisation from the UK Competent Authority; MHRA (Reference CTA 19174/0448/001-0001).

HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial participants; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the MHRA and REC within 7 days of becoming aware of the serious breach.

Insurance and Indemnity and Sponsor

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Imperial College London will act as the main Sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts taking part in the trial.

Trial Registration

The study will be registered on the ISRCTN trial registration database (Ref no: xxxx) in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

Contact with General Practitioner

It is the Investigator's responsibility to inform the participant's General Practitioner by letter that the participant is taking part in the study, and information to this effect is included in the Participant Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

Participant Confidentiality

The Investigator must ensure that the participant's confidentiality is maintained. On the eCRF or other documents submitted to the Sponsors, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the Investigator.

The Investigator shall permit direct access to participants' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

Data Protection and Participant Confidentiality

The Investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

End of Trial

For safety reporting and regulatory purposes, End of Trial will be when all study visits are complete, all data are captured on the database and the study database is declared clean and hard-locked. Participants will revert to standard asthma care.

Study Documentation and Data Storage

The Investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Participant files and other source data (including copies of protocols, eCRFs, original reports of test results, Investigational IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

14. DATA MANAGEMENT

Source Data

Source documents include original documents related to the trial, to medical treatment and to the history of the participant, and adequate source documentation must be maintained to allow reliable verification and validation of the trial data. What constitutes the source data for this trial will be outlined in the trial Monitoring Plan.

Language

eCRFs will be in English. Generic names for concomitant medications should be recorded in the eCRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the study site. Forms will be translated where appropriate.

Database

Trial data will be collected on an electronic case report form (eCRF). The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the OpenClinica database. Data is entered into the EDC system by trained site personnel. All data recorded in the eCRF will be signed off by the Investigator or his/her

appropriate designee. All changes made following initial submission of data will have an electronic audit trail with a date. Specific instructions and further details will be outlined in the study specific eCRF manual.

Data Collection

Details of procedures for eCRF completion will be provided in the eCRF guidelines manual.

Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

15. STUDY MANAGEMENT STRUCTURE

Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigator and Trial Manager. Two patient representatives will also be included on the TSC. The role of the TSC is to provide overall supervision of trial conduct and progress. The TSC will meet approximately 6 monthly throughout the duration of the trial. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-Investigators and key collaborators, community representative, trial statistician and trial manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate Terms of Reference. Two parent representatives will also be invited to join the TMG.

Data Monitoring Committee

A fully independent Data Monitoring Committee (DMC) will be set up to monitor progress, participant safety and any ethical issues involved in this trial. They will review trial progress, recruitment rates and safety data. A separate DMC Charter will be drawn up defining their responsibilities, frequency of meetings and reporting to the TSC. Meetings will be approximately every 6 months.

The statistician will analyse interim data for DMC meetings and act as data manager, in raising and resolving data queries with participating sites, via the Trial Manager. Closed DMC reports will include recruitment, randomisation balance and stratification effectiveness, baseline characteristics, withdrawals, compliance, concomitant medications, efficacy, mediators, and adverse events. Open DMC and TSC reports will be provided without outcome or arm information.

Early Discontinuation of the Study

An internal pilot will take place during the first 6 months after recruitment has started. It will use traffic light system: if the red criteria are met there will be a discussion with the Trial Steering Committee about stopping the trial.

The DMC Charter will define procedures for early termination of the study due to safety, should this be required.

Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU Head of QA in collaboration with the Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/ international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan, developed in accordance with the risk assessment.

Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be participant to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

Peer review

The trial has undergone independent peer review via the NIHR-HTA funding programme. The trial has also been reviewed by senior members of ICTU and researchers at Imperial College London.

Public Involvement

- **Involvement in development of proposal**

Asthma and Lung UK (ALUK) were closely involved in the development of the proposal and a representative from ALUK was included as a co-applicant. The study protocol and trial design was discussed with an ALUK Expert Patient Panel (EPP). Feedback from the ALUK Expert Patient Panel meeting was overwhelmingly positive and the need for a study in children using ICS-formoterol as a reliever inhaler was acknowledged as important. The panel emphasised the importance of addressing the issue of overmedication with oral

steroids in children and concerns about SABA overuse in the UK were clearly voiced. Recommendations by the EPP were incorporated into the final proposal.

- **Involvement throughout research**

The aims of active involvement of service users in this project are:

- Ensure the research is relevant to children with asthma and addresses key unmet needs of this population.
- Ensure the methods and outcome measures proposed for the study are acceptable and sensitive to the situations of potential research participants
- Support efficient and cost-effective recruitment and retention of research participants
- Support ongoing and wider public engagement with and participation in research via the communication of activities and findings of this study, and the establishment of a wider PPI paediatric severe asthma network

A representative from ALUK is one of the PI's and two co-Investigators with lived experience have been recruited to the trial management group. The PPI lead will coordinate the following activities:

Insights and impact:

Asthma and Lung UK has access to ~100,000 people with lung conditions and can use this network to generate bespoke insights that are representative for the wider population. Insights are generated via a variety of methodologies (surveys, interviews and focus groups) and these can then be used to fully understand patients' unmet need, to co-create interventions/products/solutions to be tested and to establish outcome measures of importance.

Raising awareness of the study:

ALUK's social media platforms (Facebook, Twitter, Instagram) may be used to promote the study, along with Parent Carer Network (online support group), blogs and newsletters – whichever is most appropriate. These platforms have large numbers of followers (> 55,000 on Twitter) and therefore have the potential to reach diverse populations, including children not currently managed in a secondary care centre, who may not usually have the opportunity to participate in research.

Access to expert patients (individual and panel):

ALUK convenes an Expert Patient Panel comprising patients with lung disease who have undergone training in how to support research studies as a patient. The panel has already provided input into the application and will continue to provide expertise and advise from the patient perspective, supporting and adding value to the project. Activities will include: qualitative insights on treatment approaches being investigated, feedback in terms of how the research addresses an unmet need, co-creating and developing patient-facing documentation and information; advising on recruitment/retention for the study; identifying gaps in inclusion of diverse and underserved groups throughout the study; writing and developing lay communications materials; reviewing and disseminating results; reviewing analysis and reports.

Co-design workshop with parents and young people:

ALUK will also hold a co-design workshop with parents and young people with asthma to ensure the asthma action plans used in the trial meet their needs.

Focus group:

At the end of the study, a focus group will be held with parents and children to learn more about their experiences of being participants in the study. ALUK and our public co-applicants will design and facilitate the workshop and communicate and disseminate its findings. Public co-applicants will be offered facilitation training.

Publication and Dissemination policy

The substantial output from the research will answer the question as to whether use of ICS-formoterol as a reliever in children aged ≥ 6 to <12 years, either AIR alone or as part of MART is clinically effective, cost effective and safe.

The members of the study team are well placed to ensure the results are widely and appropriately disseminated.

Results will be presented at national and international scientific meetings to both paediatric and adult respiratory, allergy and general physicians. All results will be published in high impact, general medical journals using open access policies. We anticipate several publications to arise, including the clinical effectiveness of ICS-formoterol as a reliever study and the cost effectiveness. We will communicate the results to the general public, specifically those with asthma via our PPI groups and our co-applicant at Asthma and Lung UK, will consider which of their audiences and beneficiaries would benefit most from hearing about the results before distributing them. This could involve blogs, newsletters to the Parent Carer Network (online support group) and various social media platforms. We will also use appropriate media channels via Imperial College Public Relations team to disseminate results. All participating sites will be informed of the results and encouraged to disseminate findings via their own institutional social media platforms and patient and public engagement groups.

A range of materials will be developed to support dissemination to a wide audience including parents, children, healthcare providers in primary, secondary and tertiary care, policy makers, commissioners, clinical leads in the NHS.

Other outputs will include:

- Updated national and international guidelines to extend the recommendation of ICS-formoterol as the preferred reliever to children aged ≥ 6 to <12 years
- Meta-analysis of this and other studies in younger children using ICS-formoterol as a reliever
- The heath economic analyses will either be included with these reports or in separate, more detailed evaluations
- All of these publications will be in addition to the final NIHR HTA journal report

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purposes of the study only.

It is understood by the Investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP and, therefore, may disclose it as required to other clinical Investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/ she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore, all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the Investigator(s) are completed.

Any request by site Investigators or other collaborators to access the study dataset must be formally reviewed by the TSC.

The results may be published or presented by the Investigator(s), but the Funder will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study. The results will also be submitted to the EudraCT results database in accordance with regulatory requirements.

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17. REVISION HISTORY

Version	Date	Summary of changes
1.0	24/Nov/2023	First version
2.0	21/June/2024	Substantial Amendment 1

SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: A novel reliever strategy for children with asthma: Children's Anti-inflammatory Reliever study, United Kingdom (CARE-UK)

Protocol Number: 23SM8661

Signed: _____

Dr Louise Fleming

Chief Investigator

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: A novel reliever strategy for children with asthma: Children's Anti-inflammatory Reliever study, United Kingdom (CARE-UK)

Protocol Number: 23SM8661

Signed: _____

Keith Boland
Head of Research Governance and Integrity
Imperial College London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: A novel reliever strategy for children with asthma: Children's Anti-inflammatory Reliever study, United Kingdom (CARE-UK)

Protocol Number: 23SM8661

Signed: _____

Dr Emanuela Falaschetti
Senior Statistician
Imperial College London

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: A novel reliever strategy for children with asthma: Children's Anti-inflammatory Reliever study, United Kingdom (CARE-UK)

Protocol Number: 23SM8661

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

APPENDICES

Appendix 1. MART Asthma Action Plans

MART for Step 3 Patients:

My Triggers are:

- .....
- .....
- .....
- .....
- .....
- .....
- .....

Common Triggers are:

- Viruses
- Changes in weather
- House dust mites
- Animal fur, feathers and their bedding
- Foods
- Exercise
- Upset, distress, and emotions
- Smoke – cigarettes and fires

Additional Comments:

I use Symbicort as both my maintenance and reliever therapy

Symbicort contains a medicine, called formoterol, that helps to open the airways

It works quickly so can be used if I have asthma symptoms or an asthma attack

Symbicort also contains a small dose of inhaled steroid, which helps to control my asthma and reduce the risk of an asthma attack

Your Asthma Nurse's name and telephone

.....

.....

Your Doctor's name and telephone number is:

.....

.....

Asthma and Lung UK is dedicated to improving the health and wellbeing of people with asthma. They can be contacted on the numbers below for non-study related enquiries:

Call: 0300 222 5800
Whatsapp: 07378 606 728
(Monday – Friday, 9am – 5pm, over 16 only)

My maintenance and reliever inhaler

This leaflet is intended for colour printing.

Asthma Management Plan For

.....

Date .....

CARE-UK
ASTHMA STUDY

IMPERIAL
SUPPORTED BY NIHR | National Institute for Health and Care Research

Please take this with you when you visit your doctor or asthma nurse.

1. Green zone: My every day asthma care:

- I should have few or no asthma symptoms during the day and none at night (wheeze, chest tightness, feeling breathless, cough)
- I should be doing everything I normally do (going to school, playing PE)
- If you check your Peak Flow, it is around your best

BEST PEAK FLOW .....

Green Zone Action - take your normal medications

My Maintenance and Reliver Therapy (MART inaler is Symbicort 100/3, it is a grey and red colour. It must be used with a spacer

I take 1 puff every morning and every night even when I am well.

Other asthma medications I take are:

.....

I also use Symbicort with a spacer as my reliever inhaler. I take 2 puffs when I wheeze or cough, my chest hurts or it's hard to breathe). I can also take 2 puffs before I play sports

If I am using extra doses of Symbicort most days for a week or if I need extra puffs of my reliever inhaler when I do sports or activity, I need to see my doctor or asthma nurse in the next week.

2. Amber zone: My asthma is getting worse if…

- I wheeze, cough, my chest hurts, or its hard to breathe or
- I need my reliever inhaler (Symbicort)
- I'm waking up at night because of my asthma (this is an important sign and I will book a next day appointment with my GP or nurse)

If my asthma gets worse, I will:

- **continue my normal medicines AND**
- Take 2 puffs of my Symbicort inhaler as needed to deal with my asthma symptoms
- If my asthma continues to get worse, I can take up to **12 puffs in a day** (including my morning and evening doses)
- No more than **8 puffs** should be taken on a single occasion

PEAK FLOW 1/3 DOWN .....

- **URGENT!**
- **I need to contact my doctor, nurse or other healthcare professional TODAY if**
- **My asthma symptoms are not improving despite the extra reliever doses**
- **I need to use 12 puffs of my Symbicort in a day**

3. Red zone – I am having an asthma attack if…

- My reliever inhaler isn't helping:
- I can't talk, walk or eat easily or
- I'm finding it hard to breathe or
- I'm coughing or wheezing a lot or my chest is tight/ hurts

If I have an asthma attack I will:

1. Call for help. Sit up – don't lie down. Try and keep calm.
2. Take 1 puff of my Symbicort inhaler (with my spacer) every 1 to 3 minutes up to 8 puffs
3. If I don't have my reliever inhaler, or it's not helping, or if I am worried at any time. **Call 999 for an ambulance**
4. If the ambulance has not arrived after 10 minutes and my symptoms are not improving, repeat step 2 and **contact 999 again immediately**

If you don't have your Symbicort inhaler with you and an emergency blue salbutamol inhaler is available, take one puff every 30 to 60 seconds up to a maximum of 10 puffs and call an ambulance. If the ambulance has not arrived after 10 minutes this can be repeated

Additional comments or information

Even if I start to feel better, I don't want this to happen again, so I need to see my doctor or asthma nurse today

.....

.....

.....

MART for Step 4 Patients:

My Triggers are:

- .....
- .....
- .....
- .....
- .....
- .....
- .....

Common Triggers are:

- Viruses
- Changes in weather
- House dust mites
- Animal fur, feathers and their bedding
- Foods
- Exercise
- Upset, distress, and emotions
- Smoke – cigarettes and fires

Additional Comments:

I use Symbicort as both my maintenance and reliever therapy

Symbicort contains a medicine, called formoterol, that help to open the airways

It works quickly so can be used if I have asthma symptoms or an asthma attack

Symbicort also contains a small dose of inhaled steroid, which helps to control my asthma and reduce the risk of an asthma attack

Your Asthma Nurse's name and telephone

.....

.....

Your Doctor's name and telephone number is:

.....

.....

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Whatsapp: 07378 606 728
(Monday – Friday, 9am – 5pm, over 16 only

My maintenance and reliever inhaler

This leaflet is intended for colour printing.

Asthma Management Plan For

.....

Date .....

CARE-UK
ASTHMA STUDY

IMPERIAL

SUPPORTED BY NIHR | National Institute for Health and Care Research

Please take this with you when you visit your doctor or asthma nurse.

1. Green zone: My every day asthma care:

- **I should have few or no asthma symptoms during the day and none at night (wheeze, chest tightness, feeling breathless, cough)**
- **I should be doing everything I normally do (going to school, playing PE)**
- If you check your Peak Flow, it is around your best

BEST PEAK FLOW .....

Green Zone Action - take your normal medications

My Maintenance and Reliver Therapy (MART inhaler is Symbicort 100/3, it is a grey and red colour. It must be used with a spacer

I take 2 puffs every morning and every night even when I am well.

Other asthma medications I take are: .....

.....

I also use Symbicort with a spacer as my reliever inhaler. I take 2 puffs when I wheeze or cough, my chest hurts or it's hard to breathe). I can also take 2 puffs before I play sports

If I am using extra doses of Symbicort most days for a week or if I need extra puffs of my reliever inhaler when I do sports or activity, I need to see my doctor or asthma nurse in the next week.

2. Amber zone – My asthma is getting worse if…

- I wheeze, cough, my chest hurts, or its hard to breathe or
- I need my reliever inhaler (Symbicort)
- I'm waking up at night because of my asthma (this is an important sign and I will book a next day appointment with my GP or nurse)

If my asthma gets worse, I will:

- **continue my normal medicines AND**
- Take 2 puffs of my Symbicort inhaler as needed to deal with my asthma symptoms
- If my asthma continues to get worse, I can take up to **12 puffs in a day** (including my morning and evening doses)
- No more than 8 puffs should be taken on a single occasion

PEAK FLOW 1/3 DOWN .....

- **URGENT!**
- **I need to contact my doctor, nurse or other healthcare professional TODAY if**
- **My asthma symptoms are not improving despite the extra reliever doses**
- **I need to use 12 puffs of my Symbicort in a day**

3. Red zone – I am having an asthma attack if…

- My reliever inhaler isn't helping:
- I can't talk, walk or eat easily **or**
- I'm finding it hard to breathe **or**
- I'm coughing or wheezing a lot or my chest is tight/ hurts

If I have an asthma attack I will:

1. Call for help. Sit up – don't lie down. Try and keep calm.
2. Take 1 puff of my Symbicort inhaler (with my spacer) every 1 to 3 minutes up to 8 puffs
3. If I don't have my reliever inhaler, or it's not helping, or if I am worried at any time. **Call 999 for an ambulance**
4. If the ambulance has not arrived after 10 minutes and my symptoms are not improving, repeat step 2 and **contact 999 again immediately**

If you don't have your Symbicort inhaler with you and a blue salbutamol inhaler is available, take one puff every 30 to 60 seconds up to a maximum of 10 puffs and call an ambulance. If the ambulance has not arrived after 10 minutes this can be repeated

Additional comments or information

Even if I start to feel better, I don't want this to happen again, so I need to see my doctor or asthma nurse today

.....

.....

.....

Appendix 2. AIR Only Asthma Plan for steps 1 & 2:

My Triggers are:

- .....
- .....
- .....
- .....
- .....
- .....
- .....

Common Triggers are:

- Viruses
- Changes in weather
- House dust mites
- Animal fur, feathers and their bedding
- Foods
- Exercise
- Upset, distress, and emotions
- Smoke – cigarettes and fires

Additional Comments:

I use Symbicort as my reliever therapy

Symbicort contains a medicine, called formoterol, that helps to open the airways

It works quickly so can be used if I have asthma symptoms or an asthma attack

Symbicort also contains a small dose of inhaled steroid, which helps to control my asthma and reduce the risk of an asthma attack

Your Asthma Nurse's name and telephone

.....

.....

Your Doctor's name and telephone number is:

.....

.....

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Whatsapp: 07378 606 728
(Monday – Friday, 9am – 5pm, over 16 only

My reliever inhaler

This leaflet is intended for colour printing.

Asthma Management Plan For

.....

Date .....

CARE-UK
ASTHMA STUDY

IMPERIAL
SUPPORTED BY NIHR | National Institute for Health and Care Research

Please take this with you when you visit your doctor or asthma nurse.

1. Green zone: My every day asthma care:

- **I should have few or no asthma symptoms during the day and none at night (wheeze, chest tightness, feeling breathless, cough)**
- **I should be doing everything I normally do (going to school, playing PE)**

- if you check your Peak Flow, it is around your best

BEST PEAK FLOW .....

Green Zone Action - take your normal medications

I currently only use Symbicort as a reliever and do not need to take regular doses

Other asthma medications I take are:

.....

I use Symbicort with a spacer as my reliever inhaler. I take 2 puffs when I wheeze or cough, my chest hurts or it's hard to breathe). I can also take 2 puffs before I play sports

If I am using extra doses of Symbicort most days for a week or if I need extra puffs of my reliever inhaler when I do sports or activity, I need to see my doctor or asthma nurse in the next week.

2. Amber zone – My asthma is getting worse if…

- I wheeze, cough, my chest hurts, or its hard to breathe or
- I need my reliever inhaler (Symbicort)
- I'm waking up at night because of my asthma (this is an important sign and I will book a next day appointment with my GP or nurse)

If my asthma gets worse, I will:

- **continue my normal medicines AND**
- Take 2 puffs of my Symbicort inhaler as needed to deal with my asthma symptoms
- If my asthma continues to get worse I can take up to 12 puffs in a day
- No more than 8 puffs should be taken on a single occasion

PEAK FLOW 1/3 DOWN .....

- **URGENT!**
- **I need to contact my doctor, nurse or other healthcare professional TODAY if**
- **My asthma symptoms are not improving despite the extra reliever doses**
- **I need to use 12 puffs of Symbicort in a day**

3. Red zone – I am having an asthma attack if…

- My reliever inhaler isn't helping:
- I can't talk, walk or eat easily **or**
- I'm finding it hard to breathe **or**
- I'm coughing or wheezing a lot or my chest is tight /hurts

If I have an asthma attack I will:

1. Call for help. Sit up – don't lie down. Try and keep calm.
2. Take 1 puff of my Symbicort inhaler (with my spacer) every 1 to 3 minutes up to 8 puffs
3. If I don't have my reliever inhaler, or it's not helping, or if I am worried at any time. **Call 999 for an ambulance**
4. If the ambulance has not arrived after 10 minutes and my symptoms are not improving, repeat step 2 and **contact 999 again immediately**

If you don't have your Symbicort inhaler with you and a blue salbutamol inhaler is available, take one puff every 30 to 60 seconds up to a maximum of 10 puffs and call an ambulance. If the ambulance has not arrived after 10 minutes this can be repeated

Additional comments or information

Even if I start to feel better, I don't want this to happen again, so I need to see my doctor or asthma nurse today

.....

.....

.....

Appendix 3.

Table 7. ICS and combination ICS LABA

Generic	Trade Name	Strength per dose	Indication
Beclomethasone dipropionate	Non proprietary	50/100	≥5 years
	Sobrabec	100	≥5 years
	Asmabec Clickhaler	100	≥6 years
	Clenil Modulite	50 /100	≥2 years
Budesonide	Budelin Novolizer	200	≥6 years
	Easyhaler	100/200/400	≥6 years
	Pulmicort TH	100/200/400	≥5 years
Budesonide with formoterol	Symbicort TH	100/6	≥6 years
Fluticasone propionate	Flixotide AH	50/100/200/500	≥4 years
	Flixotide Evohaler	50 / 125	≥4 years
Fluticasone with salmeterol	Seretide AH	100	≥5 years
	Seretide Evohaler	50	≥5 years
	Combisal	50/25	≥4 years

*updated information should be sought for any clinical reference