ASYMPTOMATIC

Assessing SYmptom-driven versus Maintenance Preventer Therapy for the Outpatient Management of AsThma In Children

A non-inferiority, pragmatic, randomised controlled trial using routinely collected outcome data

ASYMPTOMATIC Protocol
V4.0 05-10-23

Study Sponsor:
Alder Hey Children's NHS Foundation Trust
Institute in the Park
Eaton Road
Liverpool
L12 2AP

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UNIVERSITY OF LIVERPOOL

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This study is funded by the NIHR Health Technology Assessment Programme (NIHR130548)

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Co-Chief Investigator:

Signature: _____ **Date:** _____

Professor Ian Sinha

Consultant in paediatric respiratory medicine

Authorised by Co-Chief Investigator:

Signature: _____ _____ **Date:** _____

Professor Paula Williamson

Professor of Biostatistics

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of Sponsor:

Signature: _____ **Date:**_ _____

Kelly Davies

Research Governance and Quality Assurance Lead

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of the Lead Statistician:

Signature: _____ **Date:**__ _____

Dr Susanna Dodd

Senior Lecturer in Biostatistics

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of lead Health Economist

Signature: _____ _____ **Date:** _____

Professor Dyfrig Hughes

Professor in Pharmacoeconomics

General Information

This document describes the ASYMPTOMATIC trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre (Clinical Practice Research Datalink) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator, Ian Sinha, via the coordinating centre.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 16.

Contact Details: Institutions

Sponsor :	**Trial Management and Monitoring:**	**Health Economics:**
Alder Hey Children's NHS Foundation. Trust Clinical Research Division Institute in the Park Eaton Road Liverpool L12 2AP Tel: 0151 252 5570 E-mail: Linda.Ann.Hughes@alderhey.nhs.uk	Clinical Practice Research Datalink (CPRD) Medicines and Healthcare products Regulatory Agency 10 South Colonnade, Canary Wharf, London E14 4PU Telephone Number: +44 (0)20 3080 6383 E-mail (trial specific) studysupport@cprd.com	Centre for Health Economics and Medicines Evaluation Bangor University Ardudwy, Holyhead Road Bangor LL57 2PZ Tel: 01248 382950 E-mail: d.a.hughes@bangor.ac.uk
Statistics:	Central Study Team – Recruitment and study queries contact number	
Institute of Population Health University of Liverpool Block F Waterhouse Building 1-5 Brownlow Street Liverpool L63 3GL Telephone Number 0151 794 9752 E-mail s.r.dodd@liverpool.ac.uk	07971307807	

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	**Co-Chief Investigator**
Kelly Davies Alder Hey Children's NHS Foundation Trust Clinical Research Division Institute in the Park Eaton Road Liverpool L12 2AP Telephone number: E-mail:	Professor Ian Sinha Respiratory Unit Alder Hey Children's NHS Foundation Trust Clinical Research Division Institute in the Park Eaton Road Liverpool L12 2AP Telephone Number: 07920056469 E-mail: iansinha@liverpool.ac.uk	Professor Paula Williamson Health Data Science University of Liverpool Block F Waterhouse Building 1-5 Brownlow Street Liverpool L63 3GL Telephone Number +44 (0)151 794 9758 Email. prw@liv.ac.uk

In cases where the CI is unavailable to respond to urgent queries the following individual/s will act as cover:

Medical Expert who will Advise on Protocol Related Clinical Queries:	**Medical Expert who will Evaluate SAE Reports:**	**Medical Expert who will Evaluate SAE Reports:**
Aziz Sheikh OBE, FRSE, FMedSci Usher Institute, The University of Edinburgh, Doorway 3, Old Medical School, Teviot Place, Edinburgh, EH8 9AG, Scotland, UK and NINE Edinburgh BioQuarter, 9 Little France Road, Edinburgh EH16 4UX, Scotland, UK +44 (0)131 650 8102 Aziz.Sheikh@ed.ac.uk	**Aziz Sheikh** OBE, FRSE, FMedSci Usher Institute, The University of Edinburgh, Doorway 3, Old Medical School, Teviot Place, Edinburgh, EH8 9AG, Scotland, UK and NINE Edinburgh BioQuarter, 9 Little France Road, Edinburgh EH16 4UX, Scotland, UK +44 (0)131 650 8102 Aziz.Sheikh@ed.ac.uk	Ramiyya Tharumakunarajah Paediatric Clinical Research Fellow, Royal Preston Hospital (Sharoe Green Lane, Fulwood, Preston PR2 9HT 07971307807 ramiyya.tharumakunarajah@lthtr.nhs.uk

Additional Contacts:

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File

1 Table of Contents

2 Glossary

ACT	Asthma Control Test
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CNSGP	Clinical Negligence Scheme for General Practice
CPRD	Clinical Practice Research Datalink
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trials of an Investigational Medicinal Product
DPI	Dry Powder Inhaler
DSUR	Development Safety Update Report
ED	Emergency Department
EHR	Electronic Health Record
EMIS	Egton Medical Information Systems
EPS	Electronic Prescription Services
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GP	General Practitioner
HCP	Health Care Professional
HDRUK	Health Data Research UK
HRA	Health Research Authority
HRQL	Health Related Quality of Life
ICER	Incremental cost per QALY gained
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroids
IDSMC	Independent Data and Safety and Monitoring Committee
IPD	Individual Patient Data
IRSP	Interventional Research Services Platform
IMP	Investigational Medicinal Product
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
LABA	Long acting beta agonist
LCTU	Liverpool Clinical Trials Unit
LTRA	Leukotriene receptor antagonists
MA	Marketing Authorisation
MDI	Metered Dose Inhaler
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service

NIHR	National Institute for Health Research
NIHR CRN	National Institute for Health Research Clinical Research Network
OCS	Oral Corticosteroid
PI	Principal Investigator
PIS	Participant Information Sheet.
PROM	Patient Reported Outcome Measure
QALY	Quality-Adjusted Life Year
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCAP	Research Electronic Data Capture case report system
RSI	Reference Safety Information
SABA	Short Acting Beta Agonist
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

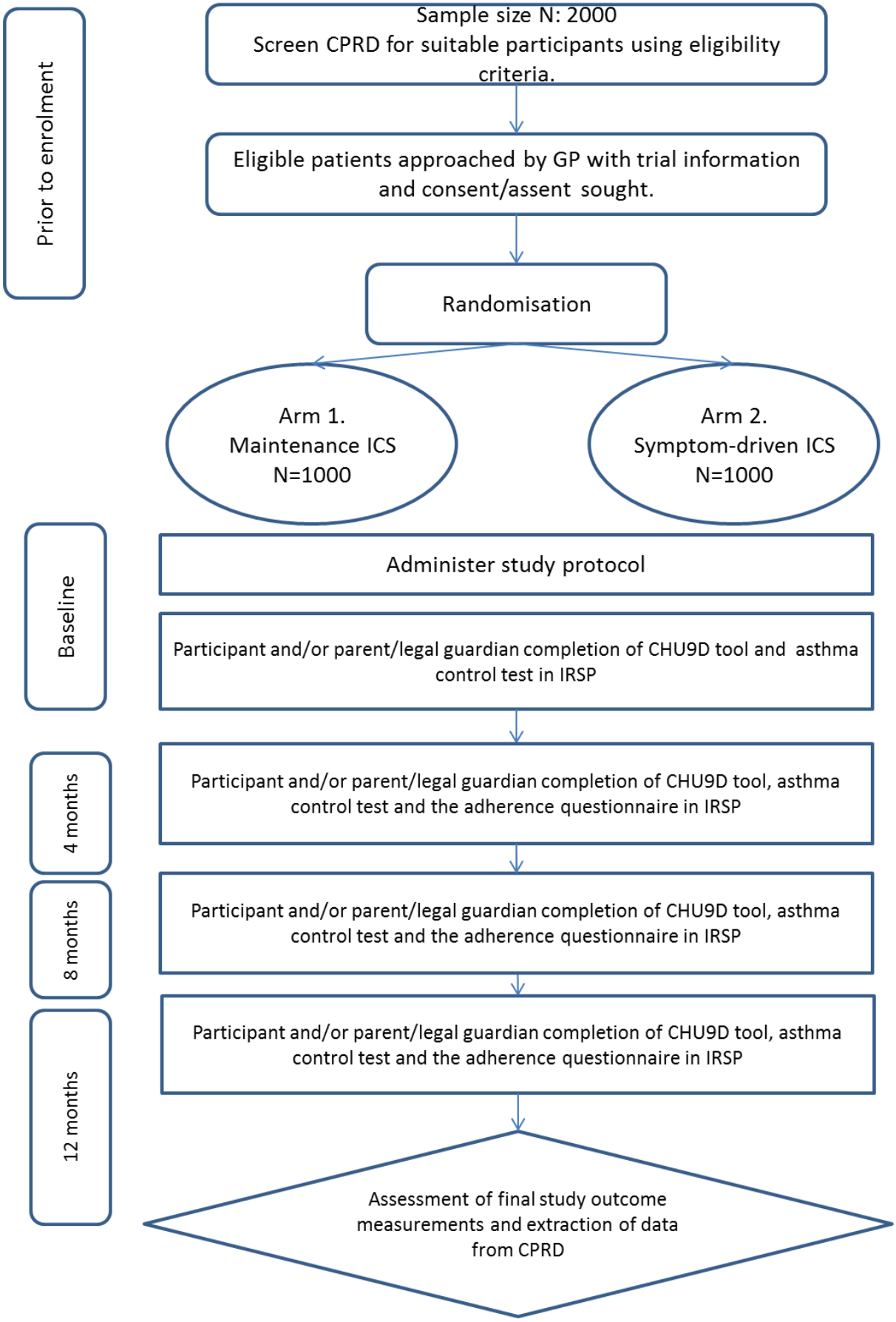
3 Protocol Overview

Full Title:	Assessing SYmptom-driven versus Maintenance Preventer Therapy for the Outpatient Management of AsThma In Children : A non-inferiority, pragmatic, randomised controlled trial using routinely collected outcome data
Acronym:	ASYMPTOMATIC
Phase:	IV
Target Population:	Children and young people aged 6-15 years, at the time of randomisation, with mild asthma who are prescribed inhaled corticosteroids (ICS) recruited from general practices across the UK that are part of the Clinical Practice Research Datalink (CPRD).
Sample size:	2000 (1000 per randomised group)
Inclusion Criteria:	Aged 6-15 years, at the time of enrolment Mild asthma At least one relevant (for asthma) prescription of short acting beta agonists (SABA) or inhaled corticosteroid (ICS) in the last 12 months (including new diagnoses). Written and informed consent and assent from the participant's parent/legal representative and participant respectively, and agreement of the parent and participant to comply with the requirements of the trial.
Exclusion Criteria:	Hospitalised for asthma in the last 12 months (this does not include children who have attended the Emergency Department but not been admitted) Three or more asthma attacks treated with oral corticosteroids in the last 12 months Significant respiratory comorbidity including cystic fibrosis, immunodeficiency or interstitial lung disease Patients prescribed or taking any of the following medications at the time of randomisation: montelukast, long acting beta agonist whether in combination with ICS or as a separate inhaler, azithromycin (given prophylactically). Patients who have previously received one or more of these treatments but

	who are no longer taking them at the time of randomisation, i.e. treatment has been stepped down, are not excluded.
Study Centres and Distribution:	UK GP practices registered with CPRD.
Patient Study Duration:	Utilising a recruitment period of 2.5 years or until 2000 participants are recruited, the follow up period will be 52 weeks per participant from the time of randomisation. **Total duration of treatment and follow up: 52 weeks**
Study Duration	54 months (01/01/2021 to 27/06/2025)
IMP / Intervention:	**Arm 1:Maintenance ICS** IMP: Beclometasone Dipropionate Fluticasone propionate Budesonide Dose: 200 mcg/24 hours, Budesonide equivalent, for 6-11 year olds, 400 mcg/24hours, Budesonide equivalent, for 12-16 year olds daily. Route: Inhaled
	Arm 2: Symptom driven ICS IMP: Beclometasone Dipropionate Fluticasone propionate Budesonide Dose: 200 mcg/24 hours, Budesonide equivalent, for 6-11 year olds, 400 mcg/24hours, Budesonide equivalent, for 12-16 year olds, on days where SABA is used. Route: Inhaled
Objectives:	
Primary:	Primary clinical outcome

	- Whether in children (aged 6 to 16 years) with mild asthma symptom-driven use of Inhaled Corticosteroid (ICS) is non-inferior to daily maintenance ICS on the risk of asthma attacks requiring oral corticosteroid (OCS). Primary health economic outcome - The cost-effectiveness (incremental cost per quality-adjusted life year, QALY gained) of symptom-driven use of ICS. Refer to section 10 for further details on outcomes to be measured
Secondary:	To determine impacts on: Time to first asthma attack requiring treatment with OCS Asthma control Unscheduled healthcare utilisation Hospitalisation Health Related Quality of Life Treatment failure Cumulative dose of ICS over the 12 month treatment period Mortality Refer to section 10 for further details on outcomes to be measured

4 Schematic of Study Design



5 Roles and Responsibilities

5.1 Sponsor

Alder Hey Children's Hospital NHS Foundation Trust is the Sponsoring organisation and is legally responsible for the study. They will formally delegate specific sponsorship roles to the Co-Chief Investigators, Clinical Practice Research Datalink and Liverpool Clinical Trials Centre.

5.2 Funder

This study is funded by the National Institute of Health Research (NIHR) Health Technology Assessment Programme.

Funder(s)	Financial and Non-financial Support Given	Role post award
NIHR Health Technology Assessment Programme	£1,597,900	This funding source provided peer review of the funding proposal via independent reviewers. The project plan included in the funding proposal has informed the protocol and study design. The Funder will not have any role during the execution of the trial, the analyses, interpretation of the data, or decision to submit results. The funder may stop the trial following review of agreed stop/amend/go criteria.

Co-Chief Investigator: Professor Ian Sinha is the Co-Chief Investigator for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Co-Chief Investigator: Professor Paula Williamson is the Co-Chief Investigator for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Principal Investigators: In each participating centre a principal investigator (PI) will be identified to be responsible for identification, recruitment and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information. The PI may also delegate specific trial tasks to appropriate trained personnel.

Clinical Practice Research Datalink (CPRD): CPRD**,** in collaboration with the Co-Chief Investigators, will have trial management responsibility as defined in the contract, and will be delegated responsibility for trial management activities including (but not limited to) study planning, Trial Master File management, safety reporting, data management, participating site coordination, implementing randomisation and monitoring.

Clinical Trials Unit: LCTC at the University of Liverpool in collaboration with the Co-Chief Investigators will be responsible for statistical analysis of trial data.

5.3 Oversight Committees

The ASYMPTOMATIC trial is subject to oversight from the following committees:

Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Co-Chief Investigators, other lead investigators (clinical and non-clinical) and members of CPRD and LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet at least monthly during setup stage and then quarterly unless more frequent meetings are required.

Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will consist of an independent chairperson (clinician/trialist), one independent expert in the field of paediatric respiratory medicine, biostatistician, trial methodologist, health economist and two public contributors including the CI and observers. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairperson. The decision for the continuation of the trial lies with the TSC. The first meeting of the TSC will take place prior to trial opening. At this meeting the TSC will agree the frequency of future meetings; these are expected to be at least annually.

Independent Data and Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) will consist of an independent chairperson, plus one independent member who is a general practitioner, and an independent biostatistician.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in Section 14.3 and 15.3 respectively.

The IDSMC will provide a recommendation to the TSC concerning the continuation of the study.

5.4 Protocol Contributors

Name	Affiliations	Contribution to protocol
Ian Sinha	Alder Hey Children's NHS Foundation Trust	Co-Chief Investigator. Study design and clinical input
Paula Williamson	University of Liverpool	Co-Chief Investigator. Study design and statistical input
Sue Beatty	CPRD	Trial management and monitoring input
Susanna Dodd	University of Liverpool	Statistical input and review of protocol
Olivia Fulton	PPI Lead	Patient and public involvement input
Christopher Griffiths	Queen Mary University of London	Co-investigator, protocol review
Jonathan Grigg	Queen Mary University of London	Co-investigator, protocol review
Nicola Harman	University of Liverpool	Protocol drafting and trial management input.
Dyfrig Hughes	Bangor University	Health economics input and review of protocol
Clare Iles	CPRD	Trial management and monitoring input
Christiane Marin	CPRD	Trial management and monitoring input
Jennifer Quint	The National Heart and Lung Institute, Imperial College London	Co-investigator, protocol review
Aziz Sheikh	The University of Edinburgh	Co-investigator, protocol review

6 INTRODUCTION

6.1 Background

Asthma affects more than a million children in the UK and preventing asthma attacks in children is a priority for the NHS[1]. Inflammation makes airways hyper-responsive, and they become narrow and productive of excess mucus when exposed to common triggers such as infection and aero-irritants (e.g. cigarette smoke and air pollution). Asthma causes cough and difficulty breathing, which worsen during acute attacks.

In the UK, admission rates from asthma attacks in children are the worst in Europe[2], and mortality rates are amongst the highest in the world[3]. Suboptimal adherence to medication, and poor understanding of what to do during an asthma attack, are common features for the 20 children each year who die from asthma in the UK[4]. In the short-term, poor asthma control has a huge impact on health related quality of life (HRQoL) and accompanying school absenteeism and parents needing to take time off from work to care for children[5]. Over the longer term, damage to the developing airway in childhood can cause lifelong problems such as chronic obstructive pulmonary disease (COPD)[6].

Fundamental changes to the management of asthma in children

One key aspect of preventing asthma attacks is to ensure children receive appropriate medication. Since the 1990s, guidelines have recommended that inhaled short acting beta agonists (SABAs) should be used as rescue treatment, and daily inhaled corticosteroids (ICS), which reduce airway inflammation, should be used to prevent symptoms and acute attacks[7]. The British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN)[7] and National Institute for Health and Care Excellence (NICE)[8] recommend long acting beta agonists (LABAs) and leukotriene receptor antagonists (LTRAs) as adjunctive preventer therapies.

The traditional approach of giving maintenance ICS in childhood asthma has been questioned by the influential Global Initiative for Asthma (GINA)[9]. Children and adults are often over-reliant on SABA without taking ICS, and this can be fatal[4]. To avoid this happening, GINA recommends not using SABA alone, and that children and adults, with mild asthma, should use ICS in a symptom-driven approach. Prescribing ICS in this way, rather than regularly, is the most radical change to asthma management since the 1980s. This GINA recommendation was in response to two randomised controlled trials (RCTs) involving adolescents and adults with mild asthma[10,11] and two subsequent RCTs have addressed similar questions[12,13]. These four trials, with 9,590 participants (including 889 adolescents), showed that symptom-driven use of ICS/LABA did not increase the risk of asthma attacks (requiring ICS, hospitalisation or visit to the emergency department) when compared with maintenance ICS and SABA, but that it may worsen asthma control (Table 1).

Table 1 - RCTs comparing maintenance ICS with SABA with symptom-driven ICL/LABA

Study	Population	Interventions	Results (regular ICS +SABA vs symptom-driven ICS/LABA)
O'Byrne 2018[10]	3849 people >12 years with mild asthma	1 Regular ICS + SABA 2 Symptom-driven ICS/LABA 3 SABA without ICS	Asthma attacks: no difference Control: ICS/LABA inferior
Bateman 2018 [11]	4215 people >12 years with mild asthma	1 Regular ICS + SABA 2 Symptom-driven ICS/LABA	Asthma attacks: ICS/LABA non-inferior Control: ICS/LABA inferior

Beasley 2019[12]	675 people >18 years with mild asthma	1 Regular ICS + SABA 2 Symptom-driven ICS/LABA 3 SABA without ICS	Asthma attacks: no difference Control: ICS/LABA inferior
Hardy 2019 [13]	890 people >18 years with mild asthma	1 Regular ICS + SABA 2 Symptom-driven ICS/LABA	Asthma attacks: ICS/lABA superior Control: no difference
Reddel et al 2021[14]	889 adolescents aged 12 to 17 years who were included in the SYGMA 1 and 2 trials (this is a subgroup analysis of the O'Byrne and Bateman studies)	1 Regular ICS + SABA 2 Symptom-driven ICS/LABA 3 SABA without ICS	Asthma attacks: no difference Control: no difference

Evidence from adult/adolescent studies in asthma is not directly generalisable to children

As outlined below, maintenance ICS may be more effective in children than adults, intermittent ICS use may be less effective in children than adults, and children use ICS and SABA in separate inhalers, which brings logistical difficulties.

i) Maintenance ICS may be more effective in children than adults: Phenotypes of asthma vary across the life course, reflecting different pathology. Children typically have inflammation patterns that respond to ICS, but some groups of adult patients do not. Smoking, high Body Mass Index (BMI), and late-onset disease are associated with steroid-resistant asthma. The prevalence of these factors in participants in the studies in Table 1 was high. For example, 26% were current or former smokers; the majority of participants in the studies reporting BMI were overweight (median BMI 27.5 [12] and 29 [13]; and most had adult-onset asthma.

ii) ***Intermittent increases in ICS may be more beneficial in adults than children:*** A 2016 Cochrane review concluded that, in adults and children, evidence did not support increasing the ICS dose during periods of poor asthma control[15]. Two RCTs have since been published. One, in 1,922 adults, found lower rates of severe asthma attacks from quadruple-dose ICS compared with usual-dose ICS during worsening asthma control (45% vs 52%, p=0.002)[16]. In 254 children aged 5 to 11 years, however, there was no difference in the effect of quintuple-dose ICS compared to usual care i.e. a fixed dose ICS regimen with no symptom driven strategy to increase dosage when asthma control is poor, on severe asthma attack rates[17]. This may be because asthma attacks in children progress more rapidly than in adults, and have different pathogenesis[18].

iii) The self-management strategy for symptom-driven ICS use is more difficult in children: For adults, GINA recommends using a combined ICS/LABA inhaler. The only ICS/LABA device available for use as reliever is a dry powder inhaler (DPI). Children and adolescents find this difficult to use, and it is not licensed for those under 12 years of age. For children, GINA recommends using ICS and SABA in separate metered dose inhalers (MDI) inhalers, through a spacer, in a symptom-driven approach. This brings logistical difficulties:

- Children and parents often underestimate symptoms, and self-management plans requiring clinical judgements can be difficult to implement.
- Taking MDI through a spacer requires slow, relaxed breathing. This is impaired when children rush, or have difficulty breathing, which causes suboptimal ICS deposition.

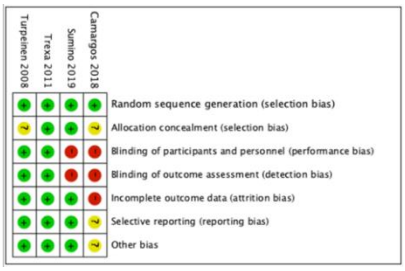
- In a symptom-driven approach, children may take ICS at the same time as SABA. This requires them to be willing (and mindful) to carry two inhalers with them. When symptomatic, they may feel they have neither the time nor the need to take ICS if they have taken SABA. Another option is to take ICS in the evening on days when SABA has been used, but this requires the child to remember to use another medication. They may not feel the need to do this if symptoms have resolved.
- Schools, who vary in their ability to care for children with asthma[19,20], have strict medication policies. Education will be needed if these plans for children included ICS.

Systematic review of RCTs comparing symptom-driven ICS strategies with maintenance ICS regimes in children with asthma

In preparing this protocol, two platforms comprising several databases (SCOPUS and the Cochrane Central Register of Controlled Trials) were searched for RCTs in children aged >6 years comparing maintenance ICS with symptom–driven ICS. Relevant ongoing studies were identified by searching the World Health Organisation (WHO) portal to trial registries. Study quality was appraised using the Cochrane Risk of Bias Tool and data were extracted for the proportion of children in each group experiencing an asthma attack requiring oral corticosteroid (OCS), and between-group differences in asthma control, Health Related Quality of Life (HRQoL) and height (reduced height velocity is a known dose-dependent side effect of ICS).

We included four completed RCTs relevant to our research question[21-24]. None of the 29 RCTs available via the WHO platform (7 of which were active) were relevant to our question. The Risk of Bias assessments are shown in Figure 1, and the studies are described below.

Figure 1 Risk of Bias assessment of the relevant RCTs (green = low risk, yellow = unclear risk, red = high risk)



(1) TURPEINEN 2008 [21]:

Population: 176 children (5-10 years) with newly diagnosed asthma, in secondary care in Finland. *Interventions: (18 month treatment period):* i) maintenance ICS (daily budesonide 400 mcg for 18 months); ii) symptom-driven ICS (daily budesonide for six months, then budesonide as needed for asthma attacks for 12 months); or iii) no ICS (disodium cromoglycate, a non-ICS preventer therapy for 18 months)All children, at times of worsening asthma control, were given higher doses of budesonide (400mcg twice daily for two weeks). *Primary outcome:* Peak Expiratory Flow Rate (a measure of airway obstruction). *Results:* *Asthma attacks requiring OCS:* 3/59 (5%) in maintenance group vs 9/58 (15.5%) in symptom-driven group (Risk difference 0.1 (95% CI 0.00, 0.21). *Asthma control:* Mean % from baseline change in asthma free days +29.2 (95%CI 21.2-37.2) in maintenance group vs +19.6 (11.8-27.4) in symptom-driven group (p=0.09). *HRQoL:* Not measured. *Height:* Mean height increase in maintenance group +5.6 cm vs +6.2 cm in symptom-driven group (p=0.019).

(2) TREXA 2011 [22]:

Population: 288 children (6-18 years) with mild asthma in five paediatric centres in the USA. *Interventions: (44 week treatment period):* i) maintenance ICS (ICS BD with placebo ICS as rescue); ii) symptom-driven ICS (twice daily placebo with ICS as rescue); combined (twice daily ICS and additional ICS as rescue); and placebo (twice daily placebo with placebo ICS as rescue). Daily ICS dose was 40mcg beclomethasone twice daily; rescue ICS dose was 80 mcg beclomethasone for every two actuations of SABA. *Primary outcome:* time to first asthma attack requiring treatment with OCS. *Results: Asthma attacks requiring OCS:* 28% (95% CI 18-40) in maintenance group vs 35% (95%CI 24-47) in symptom-driven group. *Asthma control:* No difference between groups in days with well controlled asthma (data not reported). *HRQoL:* Not measured. *Height:* Children in the maintenance group grew 1.1 cm less than those in the symptom-driven group.

(3) CAMARGOS 2018[23]:

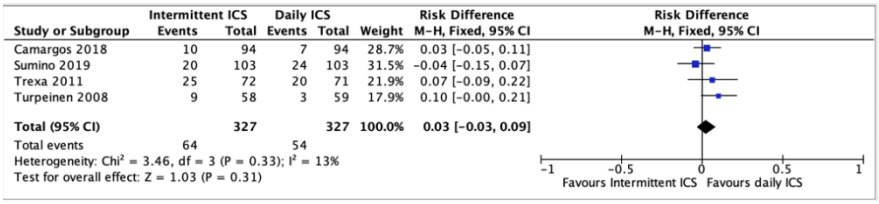
Population: 188 children (6-18 years) with well controlled asthma, treated by paediatricians and pulmonologists, in Brazil. The study did not recruit the required sample size of 282. *Interventions: (16 week treatment period):* i) Maintenance ICS (500 mcg/day beclomethasone); ii) symptom-driven ICS (1000 mcg/day with SABA for seven days upon asthma attack or worsening of symptoms). *Primary outcome:* treatment failure (an asthma attack requiring OCS). *Results: Asthma attacks requiring OCS:* 7/94 (7.4%) in the maintenance group vs 10/94 (10.6%) in the intermittent group (p=0.47). *Asthma control:* Mean Asthma Control Test (ACT) score 21.7 (SD 3.5) in maintenance group vs 22.1 (SD 3.4) in symptom-driven group (p=0.34). *HRQoL:* Not measured. *Height:* Height gain 1.4 cm (SD 1.6 cm) in maintenance group vs 1.6 cm (SD 1.4 cm) in the maintenance group (p=0.35).

(4) SUMINO 2019 [24]:

Population: 206 African-American children (6-17 years) with mild asthma, in primary care. *Interventions:* (52 week treatment period): i) maintenance ICS (beclomethasone 80-160 mcg/d); ii) symptom-driven ICS (as-needed beclomethasone 80 mg when SABA is required). *Primary outcome:* change in Asthma Control Test (ACT) score from baseline to 12 months. *Results: Asthma attacks requiring OCS:* 24/103 (23%) in maintenance ICS group vs 23/103 (19%) in the symptom-based adjustment group (p=0.62). *Asthma control:* Mean ACT score 1.55 (95% CI 0.68-2.42) in maintenance group vs 0.67 (-0.33-1.66) in symptom-driven group (p=0.1). *HRQoL*: no difference between groups in any domain. *Height:* not reported

Summary of existing evidence[21-24]; the summary of the risk of having an asthma attack requiring OCS is shown in Figure 2.

Figure 2- Proportion of children with at least one asthma attack in RCTs comparing daily vs symptom-driven ICS



It is currently unclear whether a symptom-driven approach for ICS is as safe as a maintenance approach in children in the UK. The small studies that have been done to date are heterogeneous in the ICS doses used in maintenance and symptom-driven approaches. In two studies, the symptom-driven ICS dose was higher than that licensed for children in the UK[21,23]. In the UK, most childhood asthma is managed in primary care, but only one of the existing studies was conducted in this setting[24]. The largest study was conducted in African-American children[24], which is notable because this ethnic group may be less responsive to ICS [25].

6.2 Rationale

The GINA strategy will inform the treatment of children with asthma, worldwide. The evidence from RCTs in adults and adolescents for symptom-driven ICS/LABA is not directly generalisable to children using ICS and SABA. On the basis of current evidence, it is not possible to determine whether a symptom-driven approach to ICS may increase the risk of severe asthma attacks. Given that asthma differs between children and adults/adolescents, an RCT about this fundamental aspect of care is very timely.

If a pragmatic RCT found that a symptom-driven ICS approach did not increase the risk of asthma attacks in children, this would be hugely reassuring when changing a practice that has been used globally for decades. Using less ICS would be beneficial for children, and cheaper. However, if symptom-driven ICS use increased the risk of asthma attacks, this would necessitate urgent reconsideration of international guidance. Without a trial to resolve this uncertainty there will be continuing confusion, inconsistent management and suboptimal care.

6.3 Risk and Benefits

Potential Risks

Long term daily ICS

The potential risk of daily ICS in children with mild asthma is that they might be unnecessarily exposed to side effects of long-term steroid therapy. These include local effects (oral thrush), and systemic effects (reduction in growth, abnormal adrenal gland function, and cataract). However, these systemic effects are generally not observed when using low dose ICS.

In the ASYMPTOMATIC trial, children and young people will only be recruited if they are considered, by their GP, to require ICS to manage their asthma symptoms.

The dose of ICS prescribed will be in line with current national guidelines for a low to moderate paediatric dose: ≤200 micrograms/24 hours budesonide or equivalent would be considered a paediatric low dose and 200-400 micrograms/24 hours would be considered a moderate dose.

There is no risk above that of usual care in the UK.

Symptom driven ICS

The potential risk for using symptom driven ICS is that children may be more likely to have poorly controlled asthma or an asthma attack due to under-treatment. This underpins the reason we are doing this trial, namely to examine whether intermittent, symptom-driven ICS carries an increased risk with regards children having asthma attacks.

Throughout the trial, a participant's GP will be free to amend the treatment regimen if they consider it clinically necessary irrespective of the randomised allocation. Changes to the treatment regimen will be documented in the Electronic Health Record (EHR). Safety monitoring at site via routine asthma management processes will be supplemented by regular extraction of data related to asthma exacerbation events from the EHR of trial participants. Regular extraction for safety reporting will be conducted within CPRD. Hospitalisations will be referenced against HES data annually. Data extracts from the EHR will be supplied for review by the IDSMC at intervals set by the IDSMC at their first meeting.

This study is a Clinical Trial of an Investigational Medicinal Product (CTIMP) and subject to a clinical trial authorisation by the MHRA. The MHRA will categorise the study as per the risk-adapted approach to clinical trials authorised by the MHRA.

More detail regarding management of risks associated with this trial are detailed in a separate Sponsor Risk Assessment maintained in the Trial Master File.

Potential Benefits

Children and young people often do not like having to take inhalers regularly, and worry about side effects[26] meaning that not taking a regular ICS inhaler would reduce treatment burden and inconvenience. In a symptom-driven approach, the cumulative ICS dose significantly drops to between 27%[24] and 38%[23] of a maintenance dose. This reduces the risk of dose-dependent long-term side effects on various body systems, particularly in children[27,28].

Primary Objective

This trial aims to examine whether children with mild asthma should use ICS regularly or only when they have symptoms.

The primary objective of this trial is to identify whether in children (aged 6-16 years) with mild asthma, symptom-driven use of ICS is non-inferior to daily maintenance ICS on the risk of asthma attacks requiring oral corticosteroid (OCS).

The primary economic objective is to estimate the cost-effectiveness (incremental cost per quality-adjusted life year, QALY gained) of symptom-driven use of ICS.

Secondary Objectives

Secondary objectives are to compare symptom-driven ICS with maintenance ICS with regards to:

1. Time to first asthma attack requiring treatment with OCS
2. Asthma control
3. Use of unscheduled health care
4. Hospitalisations
5. HRQoL
6. Treatment failure
7. Mortality
8. Cumulative dose of ICS over the 12 month treatment period

7 STUDY DESIGN

The ASYMPTOMATIC trial is a pragmatic non-inferiority open label RCT with a 1:1 participant allocation ratio, in general practices across the UK that are registered with the Clinical Practice Research Datalink (CPRD). Data will be obtained from EHR and approved linked datasets, using routinely collected health information, direct patient report using electronic case report form (eCRF) (accessed via CPRD's Interventional Research Services Platform, IRSP) and an eCRF for Investigators (also accessed via IRSP).

We will compare two strategies for using ICS, given over a 52-week treatment period:

(i) Arm 1 - maintenance ICS (fixed daily dose, regardless of the amount of SABA used) – this is the current standard of care
(ii) Arm 2 - symptom-driven ICS (used only on days when SABA is used for symptoms)

The primary outcome is the occurrence of at least one asthma attack requiring treatment with OCS over the 12 month treatment/follow up period. Secondary outcomes will be time to first asthma attack requiring treatment with OCS, asthma control, HRQoL, treatment failure, unscheduled healthcare utilisation, cumulative dose of ICS over the 12 month treatment period, mortality and hospitalisations. We will also undertake a cost-effectiveness analysis of the two approaches.

The ICS (beclomethasone, fluticasone, or budesonide 200 mcg/24 hours for 6-11 year olds, 400 mcg/24hours for 12-16 year olds) will be chosen by the GP, in line with their local processes, prior to randomisation and their choice of inhaler recorded in the randomisation system. ICS will be administered using a metred dose inhaler (MDI) and, if required, spacer device. A dry powder inhaler may be used for children aged 12 years and over.

Participants will be randomised to Arm 1 or Arm 2 and will receive treatment in line with the allocated arm for 12 months from randomisation. Participants will be followed up at intervals over the 12 month treatment period, using the EHR and patient reported outcome measures (PROMs) collected via IRSP and REDCap.

We aim to minimise participant attrition by using routine EHR data for follow-up outcomes without the need for additional trial specific visits.

7.1 Blinding

The Investigator is blinded to the allocation sequence, however, as an open label trial, both Investigator and participant will be aware of the allocation after randomisation. Outcome assessment is based on coded health outcomes and therefore less susceptible to assessment bias on the part of the research team. The trial statistician will remain blinded to intervention allocation from an analysis standpoint.

7.2 Study Setting

Participants will be identified and recruited from approximately 250 GP practices in the UK that are registered with CPRD. Local Clinical Research Networks (LCRN) will facilitate engagement and recruitment of trial sites where required. Follow up data collection for participants, including healthcare resource use data, will be completed using the EHR and PROMs will be completed by the trial participant/their parent/legal representative. In all other aspects, participants will follow the standard care pathway.

Selection of Participating Sites

Approximately 250 GP practices, from across England, will be required to engage in participant recruitment to meet the sample size. Criteria for the selection of trial sites will be determined by the TMG and will be described in a separate document 'ASYMPTOMATIC Recruitment Plan' maintained in the Trial Master File (TMF). In order to be selected to participate in this study, GP practices must be contributing data to the CPRD database and express an interest in recruiting participants to the trial.

Sites fulfilling the trial-specific criteria will be selected to be sites for the ASYMPTOMATIC trial and will be opened to recruitment upon successful completion of all global (e.g. REC and MHRA) and study-specific (e.g. site personnel training requirements) conditions and when all necessary documents have been returned to CPRD. Initiation of sites will be undertaken in compliance with CPRD internal processes.

Selection of Principal Investigators

Principal Investigators (PIs) will be required to demonstrate relevant experience and commitment to recruitment to the trial. All investigators will have the medical expertise necessary to conduct the study in accordance with the protocol and all regulatory and ethical requirements. Written agreement to conduct research will be obtained prior to site initiation.

PIs will be encouraged to identify a suitable co-investigator at their site, to deputise in case of PI absence.

8 ELIGIBILITY CRITERIA

The ASYMPTOMATIC trial aims to recruit 2000 patients based on sample size calculations described in Section 0.

Trial participants will be aged 6-15 years at the time of time of randomisation. Written, informed consent must be provided by the parent/guardian before any study procedures occur.

Where a participant reaches the age of 16 years during the follow up period, this will trigger a re-consent process and participants will be asked to provide consent before completing further trial assessments.

Section 11.2 contains more information regarding informed consent processes.

All participants must meet all eligibility criteria as described below.

Participants who receive a vaccination for COVID-19 will be eligible to take part in the ASYMPTOMATIC trial.

8.1 Inclusion Criteria

Patients eligible for the trial must comply with all of the following at randomisation:

1. Aged 6-15 years inclusive
2. Mild asthma, including children with a new diagnosis.
3. At least one relevant (for asthma) prescription of short acting beta agonists (SABA) or inhaled corticosteroids (ICS) in the last 12 months (including new diagnoses)
4. Written and informed consent and assent from the participant's legal representative and participant respectively (for participants under 16 years of age) and agreement of the participant to comply with the requirements of the trial.

8.1.1 Inclusion of Siblings

To avoid confusion where siblings are randomised to different intervention arms only one eligible sibling from a household should be randomised at a time. Another eligible sibling may be randomised but only after the first child has completed the 12 month intervention period.

8.2 Exclusion Criteria

Any patient meeting any of the criteria listed below at baseline will be excluded from study participation:

1. Hospitalised for asthma in the last 12 months (this does not include children who have attended the ED but not been admitted)
2. Three or more asthma attacks treated with oral corticosteroids in the last 12 months
3. Significant respiratory comorbidity including cystic fibrosis, immunodeficiency or interstitial lung disease

4. Prescribed, or taking, any of the following at the time of randomisation: montelukast, long acting beta-agonist whether in combination with ICS or as a separate inhaler, azithromycin (given prophylactically). Patients who have previously received these treatments but who are no longer receiving them at the time of randomisation i.e. treatment has been stepped down, are not excluded.

8.3 Co-enrolment Guidelines

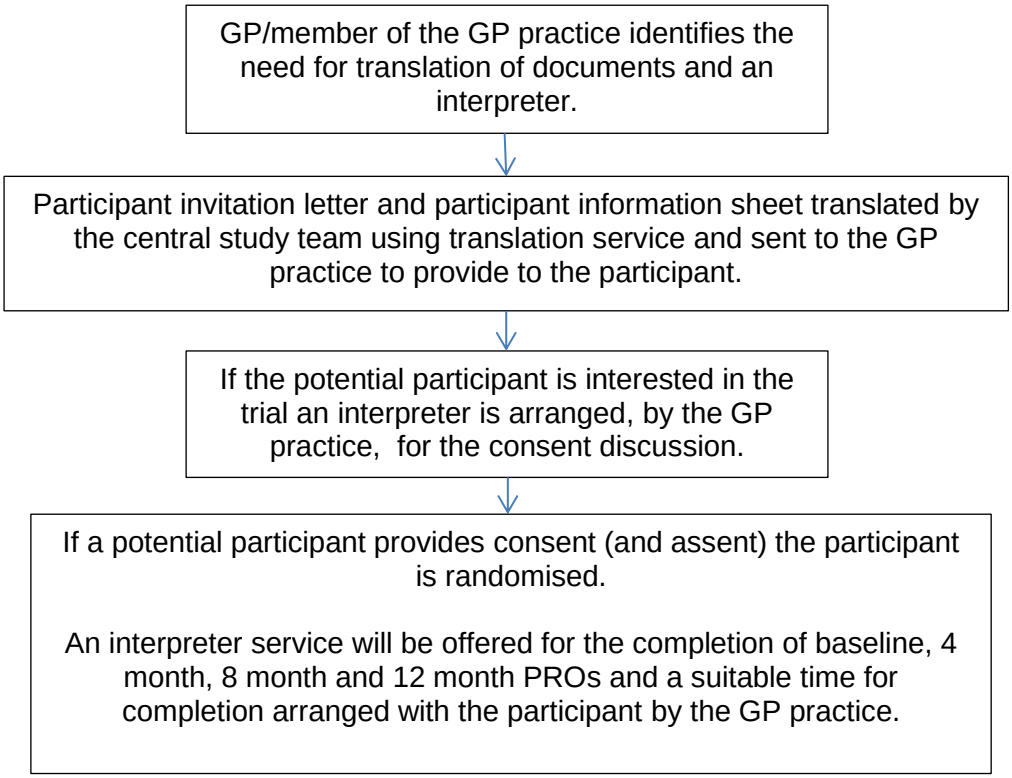
To avoid potentially confounding issues, ideally participants should not be recruited into other CTIMPs during their participation in ASYMPTOMATIC. Where recruitment into another trial is considered to be appropriate and unlikely to have any detrimental effect on the ASYMPTOMATIC trial, this must first be discussed with CPRD who will contact the Chief Investigators (Prof Ian Sinha and Prof Paula Williamson).

8.4 Translation of trial materials and use of an interpreter.

Where a potential trial participant, and/or their parent/legal representative, does not speak English, the invitation letter and participant information sheet will be translated. The GP practice will need to arrange an interpreter service for the consent discussion and to aid completion of patient reported outcomes at baseline, 4 months, 8 months and 12 months. This cost will be reimbursed by the Sponsor.

The need for translation services will be provided on an ad-hoc basis as identified by the participants' GP. Figure 3 outlines the process.

Figure 3: Provision of interpreter service and translated trial materials.



9 TRIAL TREATMENT/INTERVENTIONS

9.1 Introduction

The ASYMPTOMATIC Trial is a pragmatic trial that will use market authorised drugs within the terms of their marketing authorisation.

Eligible patients will be randomised to either Arm 1 (maintenance ICS) or Arm 2 (symptom driven ICS).

For both arms, the GP will record the ICS inhalers they intend to prescribe, in IRSP, prior to randomisation.

We will use MDI with spacer (or dry powder Inhaler, if individual adolescents prefer this) to give ICS doses within current standard practice (7). The drugs used in the trial will be prescribed, as per routine NHS practice, in formulations licenced in the UK, and dispensed by community pharmacies.

The treatment period will be 52 weeks from randomisation.

Patients in Arm 1 (maintenance ICS) will be prescribed a daily maintenance dose of ICS and patients in Arm 2 (symptom driven ICS) will be prescribed ICS only when SABA is needed.

Drug accountability will be according to standard practice for NHS prescriptions, with no additional clinical trial label. Any product recall will be managed via the usual clinical systems.

Patients will not be withdrawn from the trial if they switch to an alternative asthma treatment. Prescription data will be collected for all participants from CPRD data.

9.2 Inhaled Corticosteroids (ICS)

Arm 1 - Maintenance ICS

In Arm 1, participants will be prescribed a maintenance dose of ICS.

Patients will be prescribed one of the following at a dose of 200mcg/24hours for children aged 6-11 years and 400mcg/24hours for children aged 12 years and over.

- Beclometasone dipropionate
- Fluticasone propionate
- Budesonide

Trial participants in Arm 1 will also be prescribed a SABA inhaler, salbutamol, for use as needed in line with standard practice.

The treatment (SABA and ICS) will be provided to the patient via the usual NHS supply chain.

The trial is not restricted to a specific brand of ICS or SABA and all brands prescribed within the NHS may be used.

Trial participants prescribed an MDI will also be prescribed a UK authorised, medical spacer device in line with standard practice.

Arm 2 – Symptom Driven ICS

In Arm 2 patients will be instructed to take their ICS only on days where SABA is needed.
Patients will be prescribed one of the following at a dose of 200mcg/24hours for children aged 6-11 years and 400mcg/24hours for children aged 12 years and over.

- Beclometasone dipropionate
- Fluticasone propionate
- Budesonide

Trial participants in Arm 2 will also be prescribed a SABA inhaler, salbutamol, for use as needed in line with standard practice

The treatment (SABA and ICS) will be provided to the patient via the usual NHS supply chain.

The trial is not restricted to a specific brand of ICS or SABA and all brands prescribed within the NHS may be used.

Trial participants prescribed an MDI will also be prescribed a UK authorised, medical spacer device in line with standard practice.

9.3 Manufacturing and Distribution

Intervention supplies will be off the shelf sourced from usual NHS stock, with no modifications to packaging.

Drug accountability will be according to standard practice for NHS prescriptions. Any product recall will be managed via the usual clinical systems.

9.4 Preparation, Dosage and Administration

An MDI will be prescribed to give doses within current standard practice. Alternatively a dry powder inhaler may also be prescribed if individual adolescents prefer this[7]. The choice of ICS inhaler will be at the GP's discretion. The GP will record which ICS inhaler they intend to prescribe before randomisation.

Children randomised to the maintenance ICS group will be prescribed ICS twice daily, to be taken regardless of the level of symptoms (Beclometasone dipropionate, Fluticasone propionate, or Budesonide 200 mcg/24 hours for 6-11 year olds, 400 mcg/24hours for 12-16 year olds).

Children randomised to the symptom driven ICS group will be prescribed an ICS inhaler, to be taken on days when SABA is required for symptom relief. In a 24-hour period with no symptoms requiring SABA, they should have no ICS; if SABA has been required, they would take ICS (Beclomethasone, Fluticasone propionate or Budesonide up to 200 mcg/24 hours for 6-11 year olds, 400 mcg/24hours for 12-16 year olds).

Children and parents could achieve this in the following ways, depending on what they feel works best for their circumstances at the time:

- On days that a patient has symptoms requiring SABA use their ICS should also be taken, up to four times that day (or over the following 24 hours) – usually taken as 2 puffs twice daily.

- If SABA is used overnight, the prescribed dose of ICS should be started in the morning.

- If SABA is required during the day, the prescribed dose of ICS should be started in the evening.

If the child pre-emptively takes SABA before exercise, this would not necessitate ICS that day.

ICS will be prescribed by the GP and dispensed by a community pharmacy as per standard practice.

ICS will be self-administered at home or school if needed.

The GP may also prescribe an appropriate, UK authorised, medical spacer device in line with standard practice.

In both treatment arms, SABA will be prescribed by the GP and dispensed by a community pharmacy as per standard practice.

Unused ICS or SABA should be disposed of in line with local standard practice.

9.5 Treatment Modifications

After the patient has entered the trial, the clinician is free to give alternative treatment/intervention to that specified in the protocol, at any stage, if they feel it to be in the best interest of the patient.

The reason for treatment modifications, including treatment escalation, will be recorded in the EHR and the patient will remain within the trial for the purpose of follow-up and data analysis according to their randomised treatment. Similarly, the parent/legal representative or participant (aged 16 years and over) remains free to

withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing further treatment (see section 10.8). If treatment escalation is needed, this should be done in line with current standard clinical practice.

9.6 Assessment of Compliance

Given that poor study conduct quality (including eligibility violations, poor adherence, treatment crossovers and missing data) typically leads to a dilution of the treatment effect, and thus an increased probability of falsely concluding non-inferiority, we will supplement intention to treat analyses with appropriate causal methods to adjust for treatment crossovers rather than rely on per protocol or as treated analyses (which are typically subject to selection biases). We will facilitate this analysis using the following methods to assess adherence:

Patient reported adherence: A questionnaire will be completed via REDCap to collect information on adherence to treatment and treatment switching (for example, if patients randomised to the daily maintenance arm (Arm 1) decide to stop taking ICS each day and instead start taking ICS only on days that they need to take SABA, or if patients randomised to the symptom driven arm (Arm 2) decide to start taking ICS each day). Parents will be encouraged to complete the adherence questionnaire with their child. The questionnaire will ask whether their child has switched from their assigned treatment regimen to the alternative (and if so, when they switched from their assigned treatment).

Objectively assessed patient adherence. Patients' adherence will be assessed objectively using CPRD prescription data and records of community-dispensed medicines available from NHS Business Services Authority (NHSBSA), if available as a standard linkage at time of analysis. Prescription and/or dispensing data will be summarised into continuous multiple-interval measures of medication availability/gaps. We will perform sensitivity analyses (detailed in the statistical analysis plan) to explore causal effects based on these adherence metrics derived from the prescription/dispensing data.

<u>Contamination between treatment groups</u>
We will aim to minimise possible contamination between treatment groups through both communication and monitoring strategies.

Communication:
The importance of the trial, adherence to the allocated intervention and completion of data through REDCap will be explained on all participant information, including the patient information sheet.

Communication with GPs will be maintained using a trial newsletter that will include information about trial recruitment and trial issues that may need attention (such as adherence).

Central Monitoring of compliance: The ordering of repeat medication through the prescription generating and issuing channels is likely to vary between practices, and will be affected by the use of electronic prescription services (EPS) whereby GPs issue scripts direct to pharmacies.

A patient on a repeat ICS prescription who repeatedly requests the prescription early (suggesting overuse) would be flagged in the GP system and picked up through a variety of routes: by prescribing clerks; through a system in which parameters are set for when another prescription can be issued such that it would not be possible for the receptionist to print it off if someone ordered a prescription more quickly than expected and so the request would come to a prescriber to review; or during the patient's asthma review by the asthma nurse. This would often be raised as a query with one of the GPs before issue. The GP may ask the patient to arrange a telephone consultation to discuss if this was a concern.

Interim and final analysis:

(i) Adherence and contamination will be reviewed as part of the interim and final analyses, using a combination of these trial-specific metrics and routine care monitoring indicators, namely patient-reported adherence (including switching between treatment allocation groups), adherence metrics from prescription/dispensing records and GP notifications

9.7 Concomitant Medications/Treatments and Specific Restrictions

9.7.1 Medications Permitted

All medications other than those listed below are permitted.

9.7.2 Medications Not Permitted/ Precautions Required

The following medications are not permitted at the time of enrolment:

Montelukast

Long acting beta-agonist in combination inhaler with ICS

Azithromycin prescribed prophylactically.

Maintenance OCS

Omalizumab and other biologicals

Theophylline

All medications above are permitted should the participant require treatment escalation at any point following enrolment.

9.7.3 Data on Concomitant Medication

Data will be collected on medication prescribed for the treatment of eczema, hay fever or allergic rhinitis. These data will be captured via the EHR, reported as a secondary outcome and extracted from the linked data on community-dispensed medicines from NHSBSA.

The IMP in the ASYMPTOMATIC trial is not known to interact with the current approved COVID-19 vaccines. Where a trial participant receives the COVID-19 vaccine this will be considered as a simple concomitant medication with the date and type of vaccine recorded in the patient's EHR.

9.8 Overdose

Overdose is unlikely to occur. For example, one inhaler typically contains 200 x 200mcg doses. If all 200 doses were taken at the same time, the dose would be equivalent to one dose of oral corticosteroids.

10 OUTCOMES

10.1 Primary Outcome

The primary efficacy outcome is the occurrence of at least one asthma attack requiring treatment with OCS in the 12-months after randomisation. Information on this outcome will be obtained from prescription records and through linkage with Hospital Episode Statistic (HES) data.

The primary economic outcome is the incremental cost per QALY gained (ICER) over the 12 month treatment/follow up period.

Outcome consideration	**Incremental cost per QALY gained**
Specific measurement variable	CHU-9D questionnaire responses Resource use from HES and CPRD data
Participant-level analysis metric	For utilities: application of UK tariff scores For QALYs: area under the utility-time curve For costs: sum-product of all measured items of resource use and their respective NHS unit costs
Method of aggregation	ICER calculated as the difference in total costs between intervention groups, divided by the difference in QALYs.
Time point of specific measurement variable	CHU-9D at baseline, 4, 8- and 12-months Resource use at the end of the trial

10.2 Secondary Outcomes

Secondary outcomes at 4, 8 and 12 months after randomisation, to be collected via IRSP, will be Asthma Control Test (ACT) scores, participant adherence to the intervention (adherence questionnaire) and health utility (CHU9D tool). Outcomes relating to treatment include cumulative dose of ICS (estimated from the number of ICS inhalers prescribed, as indicated from prescription records) and treatment failure (i.e. when LABA or LTRA additional preventer therapies were prescribed, as determined from prescription records). Hospitalisation and mortality will be identified from linked HES data.

Asthma attacks requiring OCS in GP or hospital setting in the 12-months after randomisation (primary outcome): Data will be collected from prescription records which are accurate and easy to search. The 12-month treatment period accounts for seasonal variation in asthma attacks. CPRD will link to Hospital Episode Statistics (HES) data to identify Emergency Department (ED) attendance. All children who attend ED with asthma should, according to national guidelines, receive OCS[7]. We may miss a small number of children who attend walk-in-centres or out-of-hours GP services, because these are not all linked to GP records. At each of the follow up time points (4, 8 and 12 months), participants will be asked if they have attended a walk-in-centre or out-of-hours GP service in the preceding months.

Time to first asthma attack requiring treatment with OCS: The date of first asthma attack requiring treatment with OCS will be collected from prescription records and HES data, in order to inform analysis of the time to first asthma attack requiring treatment with OCS from date of randomisation.

Asthma Control Test[29]: This Patient Reported Outcome Measure (PROM) is simple, validated, and widely used in asthma studies in children[(40).] According to NICE this should be measured annually, and be available as routinely collected data. As this is variable, we will also ask parents to complete it at baseline, 4, 8 and 12 months after randomisation, via IRSP.

Adherence: We will collect patient reported data on adherence to the randomised intervention. Adherence will be collected at 4, 8 and 12 months after randomisation using the adherence questionnaire.

Cumulative dose of ICS: This will be measured using prescription records to identify the number of ICS inhalers used in each group. As we know the number of inhalations in each inhaler, we can estimate the total dose used over the 12-month study period.

Treatment failure: We will search prescription records to identify children started on LABA or LTRA additional preventer therapies. This would constitute treatment failure.

Mortality: We will identify death by linking CPRD and Office of National Statistics (ONS) data.

Safety: We will ask GPs to report Serious Adverse Events (SAEs). SAEs will be reviewed by the CI and Suspected Unexpected Serious Adverse Reactions (SUSARs) reported accordingly. Periodically, we will prepare a safety report from CPRD data to check that all potential SAEs have been reported.

Health economics:

Resource use: Data on hospitalisations will be extracted from the EHR or via linkage with HES data. In around 70-75% of practices included in CPRD, hospitalisation is linked to GP data. Data on patients' use of primary care services will be extracted from CPRD. The cost of community-dispensed medicines will be derived from linked NHSBSA data.

Health utility: We will measure this using the CHU9D tool[30]. This generic multi-attribute, preference-based utility measure is validated in children and can be used to calculate Quality-Adjusted Life Years [31,32]. This is not routinely collected in practice, and it will be completed by participants and their parents via the IRSP at baseline and at 4, 8 and 12 months after randomisation.

Objectives	Data Sources	Time point(s) of evaluation
Efficacy:		
Primary: To determine whether the symptom-driven use of ICS is non-inferior to daily maintenance ICS on the risk of asthma attacks requiring OCS.	The number of oral corticosteroid prescriptions HES data - ED visits for asthma attack	12 months

To determine the impact of symptom driven or maintenance ICS on asthma control	Asthma control test (patient reported outcome measure)	Baseline, 4 months, 8 months and 12 months
To determine the cumulative dose of ICS	The number of prescribed ICS inhalers and dose.	12 months
To determine treatment failure defined as LABA or LTRA additional preventer therapies	Prescribed LABA or LTRA	12 months
Safety:		
Serious adverse events	Assessment of related adverse events	Monthly
SUSARS	Assessment of SUSARs	Monthly
To determine mortality	Death	12 months
Hospitalisations	Hospitalisation	12 months
Health Economics:		
To determine the impact of symptom driven or maintenance ICS on the dimensions of CHU-9D	CHU9D (patient reported outcome measure)	Baseline, 4 months, 8 months and 12 months.
To determine healthcare resource use	Resource use primary and secondary care service contacts, and medicines prescribed	12 months
Other objectives:		
Atopy – to determine in a subgroup analysis whether children are also treated for eczema, hay fever and allergic rhinitis	Prescribed treatment, including corticosteroids or antihistamines, before or during participation in the trial.	12 months
To determine adherence to the intervention	Adherence questionnaire- self-report adherence instrument completed via REDCap	4 months, 8 months and 12 months.

11 PARTICIPANT TIMELINES AND ASSESSMENTS

An overview of the participant pathway is provided in figure 4 – figure 4 updated to include expression of interest form, e consent and PROMs using REDCap

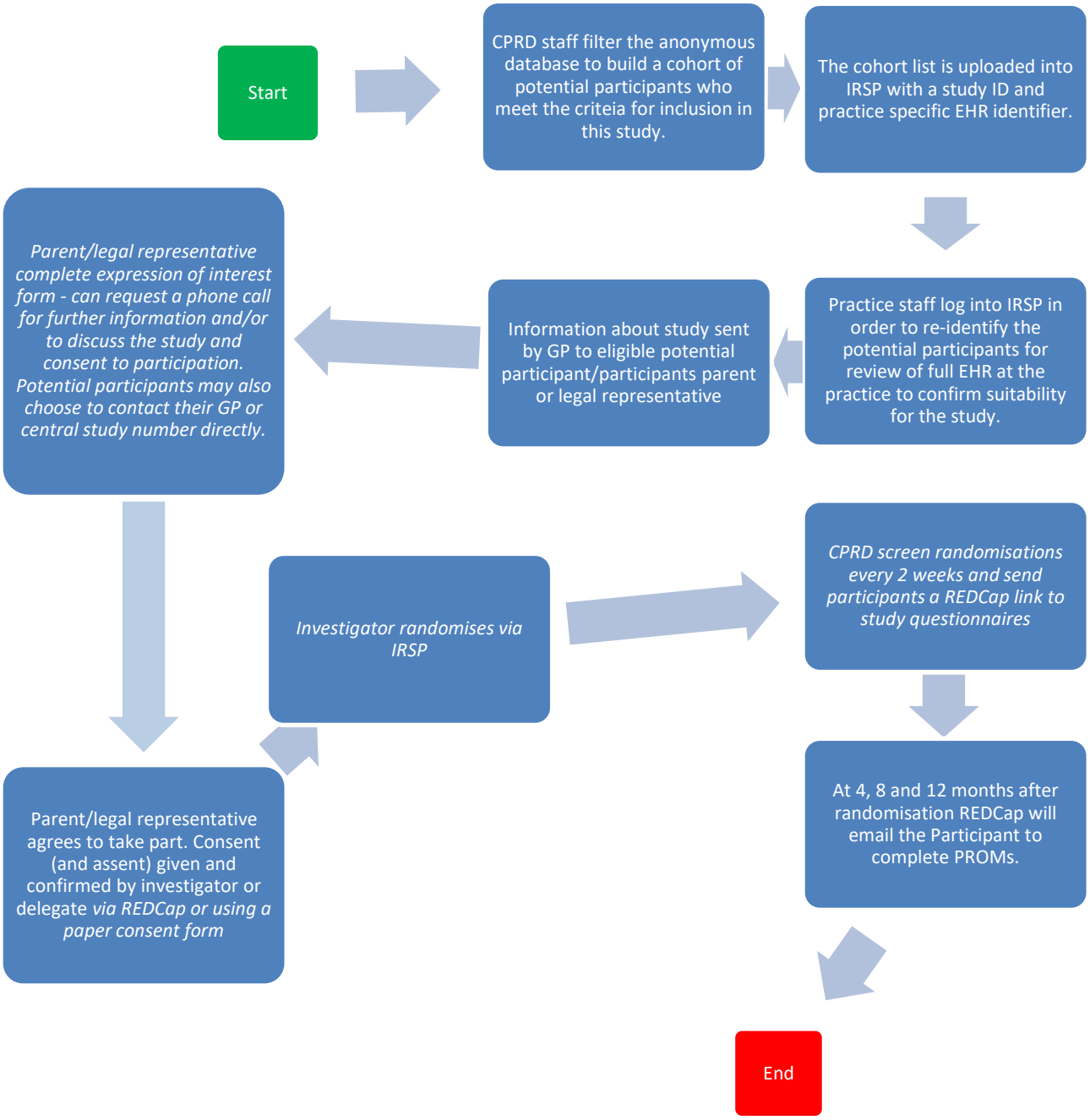


Figure 4. Participant pathway.

11.1 Participant Identification and Screening

CPRD is funded by the National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). It harnesses data from EHRs of patients in general practices in the UK using Egton Medical Information Systems (EMIS) or Vision software. It is one of the world's largest databases of longitudinal primary care medical records. It includes 16 million patients who are demographically representative of the UK population[33], with coverage exceeding 1 in 4 UK GPs. CPRD has been successfully used for influential epidemiological research in asthma[33-35]. CPRD maintains confidentiality of all patient data according to CPRD internal governance and in line with the Data Protection Act 2018

Children diagnosed with asthma and treated with ICS will be located through filtering the CPRD database, using validated codes[34] in predefined code lists. We will include children with at least one asthma-related observation and one relevant prescription of SABA or ICS coded into the GP record in the previous 12 months. This will generate pseudonymised patient lists specific to each Primary Care practice which can be loaded into the IRSP for the Investigators to access and identify the patients for review. The trial adopts a pragmatic approach to the pre-screening criteria, aiming to display to Investigators only those patients who are likely to fulfil enrolment criteria.

The patient list will be reviewed by a study approved health professional at the site who will respond to a specified set of screening questions to ensure that only eligible patients are invited to participate. For patients meeting the selection criteria, the Primary Care team will send an invitation to their parent/legal representative informing them about the study. This invitation may be sent electronically or by letter. The invitation will include either a copy of or links to the relevant participant information sheets (PIS) together with the Participant Information Sheet (PIS). This will allow potential participants and their parents/legal representatives the opportunity to consider whether they would like to take part in the study.The invitation will also contain a central contact number and GP practice contact details to that the parent/legal representative is able to arrange a discussion about the study. An expression of interest form hosted on REDCap may also be used and a link included in the invitation.

CPRD will repeat the database search and update the potential participant list for each practice in IRSP on a regular basis to include those who newly meet the inclusion criteria while the trial is recruiting.

An anonymised log of patients who are assessed for eligibility but not invited or randomised will be maintained in IRSP and data on recruitment rate reported to the TMG. The potential participant list provided to practices via IRSP will document patient status including those who have declined consent, . Patients who decline to participate are removed from consideration in the future and are not approached again.

Study training will be coordinated by CPRD, it will be available to designated research staff for completion in the IRSP, patient lists are not available for review until study training has been completed.

11.2 **Informed Consent**

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site. The Site Principal Investigator retains overall responsibility for the conduct of research at their site; this includes the obtaining

of informed consent for participants at their site. The Site Principal Investigator must ensure that any person delegated responsibility to participate in the informed consent process (such as Practice Nurses or CRN Research Nurses) are duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. The consent discussion may also be completed centrally by appropriately trained study staff who have completed GCP and been added to a central study delegation log. The consent process includes explicit consent for the transfer of identifiable information on the consent form itself.

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Documented informed consent is required for all patients participating in the ASYMPTOMATIC trial. Participants in the ASYMPTOMATIC trial will be under 16 years old at the time of enrolment and considered minors. Proxy consent from a parent/legal representative will be sought together with participant assent. The process will involve discussion between the potential parent/legal representative, participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for parents/legal representatives and potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Where, during their follow up period, participants make contact with their GP practice in relation to their participation their informed consent will be re-affirmed and all discussions and consent should be documented appropriately. If a parent/legal representative does not want to provide consent for their child, they may be asked if they would like to provide a reason but do not have to give one.

11.2.1 Prospective Informed Consent and Assent Process

Appendix 1 outlines the consent process.

Documented informed consent will be sought from persons with parental responsibility who will be approached by the study team and invited to consider participation.

Persons with parental responsibility will be approached by their GP practice and provided with study information by post, email or SMS. The preferred method for initial contact will be by post with hard copies of the information sheets and consent forms provided to potential participants. his information will include the PIS and a covering letter/email, in the case of the SMS this will be provided via a link in the SMS. The information sheet will include a detailed explanation of the study and make clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected.

Expression of Interest to Take Part

If interested in taking part the parent/legal representative of the potential participant will be asked to notify their GP practice or contact the central study number. We will also provide a link to an expression of interest form that can be used by the parent/legal representative to request a follow up appointment to discuss the

study or to decline participation. The expression of interest form will be available online, accessed using a quick response code (QR code) or a link included in the letter/email/SMS.
The expression of interest form will ask participants to provide information that allows documentation of their response. This will as a minimum include the name of their GP practice, child's initials and year of birth.. If they decline the study only this data will be recorded, it will be used to document that the participant has declined so that no further invitations are issued. If the participant is interested in taking part and would like to discuss the study the form will also collect their name, contact details and best time to contact them.

Direct contact with the GP or central study number

Participants may also contact their GP (or other delegated member of practice staff) or the central study contact directly without completing the expression of interest form. Contact details are provided in the invitation letter/email.

Follow up of invited participants
If no response has been received, the GP practice, where possible, will telephone the parent/legal representative to confirm that they have received the information and to ask if they would like to make an appointment to discuss taking part.

Trial discussion

The appointment to discuss the trial may be face to face, by telephone or web-based (video call). The GP, or delegated other, will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise. This discussion may also take place with a clinically trained member of the central study team.

After verbal and written information has been provided, the individual seeking consent will ensure that the person with parental responsibility, has fully understood all the information and will ask if they are happy to consent to participation in the trial. They will also discuss whether their child is able and would like to provide written assent.

Consent and Assent
Following the trial discussion, the person with parental responsibility for the participant will be asked to provide informed consent. The consent form may be provided as a paper copy or electronically (eConsent) using REDCap. To aid accessibility parents will also be offered the option for consent and assent to be completed by telephone. Where this is the case the person, with appropriately delegated responsibility, will complete a paper consent form during the consent discussion. They will specifically document that the consent was completed by phone and countersign the consent form. A copy of the completed will then be sent to the parent. The consent form will be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

All minors aged 6 years and above will be approached for assent. The trial discussion will include discussion about the trial, supported by age appropriate participant information, plus discussion about whether the child is able and would like to provide written assent. Where a minor is approached for assent, they will not be entered into the study until assent (in addition to legal consent from an appropriate adult) is provided. An exception to this is made where the minor expresses a wish for the decision to be made solely by the appropriate adult and this should be documented.

The age appropriate REC approved assent form will be provided either as a hard copy or electronically using REDCap. Assent may also be recorded by telephone and a paper copy of the consent form completed on the participant's behalf by an appropriately delegated member of the trial team.

Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative. Assent should be obtained where appropriate and documented in the patient notes. Where a child is unable to give written assent, this will be documented in IRSP, and REDCap where eConsent is used.

Documenting Consent and Assent

Confirmation of consent should be documented in IRSP prior to proceeding to randomisation

Paper consent and/or assent form

The consent form and assent form will be retained in the trial site's Investigator Site File (ISF) and the following copies will be made:

- One copy provided to the person with parental responsibility for the participant's information.
- One copy transferred to the CPRD by secure email.
- One copy filed in the participant's medical records (electronic).

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.

Electronic consent/assent

Consent and assent collected via RED-CAP will collect an electronic signature of the parent. Once completed the investigator or delegate(s) will sign and date their portion of the electronic consent form and add the participant's study IDr.

Upon completion a PDF of the e-consent form will be generated and the following copies made:

- One copy provided to the person with parental responsibility for the participant's information.
- One copy transferred to the CPRD by secure email.
- One copy filed in the participant's medical records (electronic).

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.

11.2.2 Participants reaching 16 years after enrolment

Participants aged 15 years at the time of enrolment may turn 16 during the treatment/follow-up period. Where this is the case, the participant will be asked to consent for their continued involvement. CPRD will monitor the patient's age and notify their GP practice when consent is required. The GP practice will send a consent form along with a short information sheet explaining the reason for this consent to the patient. The short information sheet will highlight any changes in participation, for example, that the participant may choose to be emailed future links for PRO completion directly. The consent form may be sent as a paper copy or as e-consent using REDCap.

11.2.3 Eligibility Assessment and Confirmation

Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log. Eligibility should be reviewed using patient notes and confirmed during the discussion with potential participants. Eligibility criteria are described in detail in Section 0.

Screening of participants will take place in line with section 11.1. Eligibility will be assessed and confirmed by an appropriately delegated study team member following the informed consent discussion and consent to participate has been obtained.

Eligibility confirmation must be documented in the participant's EHR and on the Eligibility CRF in IRSP. Details must include at a minimum who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (e.g. randomisation). Details will also include a "Read" and "SNOMED" code to record participation in the ASYMPTOMATIC trial and allow this to be searchable on the CPRD.

11.3 Baseline Assessments

There are no baseline assessments for the PI to complete. Fully executed consent (signed by parent/legal representative and co-signed by PI) will allow the GP to progress to randomisation. Randomisation in IRSP will trigger an email which will send the baseline assessments of the patient reported outcome measures to the email address registered for the participant.

No baseline assessments are required prior to randomisation; rather randomisation will trigger an email to the participant to complete the relevant PROMs in IRSP.

Baseline data will be collected from the EHR and from patient reported outcomes. Baseline assessments include:

- Asthma Control Test
- CHU9D (health related quality of life questionnaire)

11.4 Randomisation / Registration

Implementation: The CPRD IRSP includes a module for randomisation once informed consent and selection criteria have been confirmed. The patient is assigned a unique randomisation number, which is automatically allocated by the IRSP.

The treatment allocation will be reported in IRSP and the prescription logged in the EHR as per usual practice.

In detail:

a) Participants will be enrolled into the trial during routine clinical practice. Eligible patients must meet all eligibility criteria.
b) The Investigator (or appropriately qualified and trained medical professional) will:
   - Determine patient eligibility for participation in the trial
   - Obtain written/electronic informed consent from a person with parental responsibility before any trial specific procedures are performed.
   - Obtain assent from the trial participant or document reasons why assent was not obtained.
   - Record which inhalers (ICS and SABA) they intend to prescribe.
c) The participant is enrolled into the trial via the web based Clinical Research Practice Datalink (CPRD) Interventional Research Services Platform (IRSP), and on confirmation of eligibility, and the confirmed provision of informed consent, is automatically randomised to either the maintenance or symptom driven via IRSP.
d) The participant is assigned a unique randomisation number which is automatically added to the patient record on IRSP.
e) If allocated to Arm 1 (maintenance ICS) the Investigator will ensure ongoing supply of an appropriate ICS for daily use in line with clinical practice for maintenance ICS. Dosing instructions will clearly state daily use of the ICS.
f) If allocated to Arm 2 (symptom driven ICS), the Investigator will ensure ongoing supply of an appropriate ICS in line with clinical requirements and local guidelines for prescribing. The dosing instructions will clearly state the conditions under which the ICS should be used (i.e. when short acting beta agonist (SABA) are required for symptom control).
g) The treatment allocation is recorded on IRSP and in the participant's electronic health record (EHR) along with the drug prescribed.
h) Randomisation may take place at any convenient time.
i) As the trial is unblinded, there is no requirement for access to randomisation codes out of hours or in an emergency situation.
j) If a participant withdraws from participation in the study, their randomisation code cannot be reused.

Statistical software: The randomisation sequence will be generated using Stata® 15.1 (StataCorp LP, Texas).

Concealment of allocation: The Investigator is blinded to the allocation sequence, however, as an open label trial, both the Investigator and participant will be aware of the allocation post randomisation.

Out-of-hours access to randomisation codes: There is no requirement to access randomisation codes out of hours or in an emergency situation in this trial.

Procedures for handling incorrectly enrolled or randomised participants: Participants who fail to meet the eligibility criteria should not, under any circumstances, be enrolled. Eligibility should be checked prior to consent and randomisation. Where a participant does not meet all the eligibility criteria but is randomised in error, the Investigator should inform the Sponsor (or delegate) immediately, and a discussion should occur between the Sponsor (or delegate) and the Investigator regarding whether to continue or discontinue the patient from treatment. The Sponsor (or delegate) must ensure all decisions are appropriately documented.

Procedure where a participant withdraws from the trial: If a participant withdraws from participation in the study, then their randomisation code cannot be reused. No additional patients will be recruited to the trial to replace those patients withdrawn or lost to follow up.

11.4.1 Randomisation Process

Participants will be randomised via the IRSP, which possesses a randomisation system, to receive either Arm 1 (maintenance ICS) or Arm 2 (symptom driven ICS) in a ratio of 1:1. There will be no stratification. The sequence of treatments will be randomly permuted in blocks of several randomly varying sizes. Randomisation will take place as soon as possible after eligibility is confirmed and written consent given. Randomisation should only take place once:

a) Eligibility criteria have been fulfilled (and eligibility confirmed)
b) Fully informed written consent/proxy consent, and assent where appropriate, has been obtained (and appropriately countersigned)

The baseline page of IRSP has been completed by the PI/delegated staff member.

A personal login username and password, provided by CPRD, will be required to access IRSP and therefore the randomization system.

Once the patient is randomised to one of the treatment arms, the IRSP will allocate a unique study randomisation number, which will be displayed to the Principal Investigator/delegated research staff at site and added to the participant record within IRSP, available to the Trial Coordinator/ Monitor on the study dashboard.

Note that: the IRSP does not generate an automatic email confirmation upon randomisation.

Following allocation, participants should be notified of their allocation as soon as possible and receive their randomised treatment allocation as described in Section 9

CPRD will regularly monitor randomisation events.

11.4.2 Randomisation System Failure

Where the Investigator is unable to access IRSP for randomisation the following actions should be taken:

1. The Investigator will report the issue to studysupport@cprd.com
2. CPRD will raise a live urgent support ticket.

3. CPRD will maintain communication with the Investigator to inform them of the status of the resolution.
4. As soon as the issue is resolved the Investigator will be able to access IRSP to complete the randomisation process.
5. The patient will then be informed of the allocation, and where required, prescription of the allocated treatment will be carried out as per usual clinical practice.

11.5 Intervention

Once the research team are made aware of the treatment allocation, participants will receive a prescription for their allocated treatment and instructions for use. Participants should be advised to adopt their allocated treatment as soon as possible, ideally within 24 hours.

11.6 Schedule for Assessments and Follow-up

All assessments and follow up are to be conducted in line with the Schedule of Assessments below:

Schedule of Assessments:				Follow up schedule.			
Procedures		Screening	Baseline	4 months	8 months	12 months	4 weeks post study Completion
Filter of practice EHR to locate potentially suitable participants (CPRD)		X					
Review of practice cohort for suitability for trial invitation of suitable patients (Practice)		X					
GP or delegated personnel contact with parents to discuss the trial (telephone)		X					
Eligibility confirmed by GP or delegated clinicianor allied health professional (telephone/video call/face to face)		X					
Signed Consent (and assent) Form (paper, telephone consent or electronic)		X					
Randomisation			X				
Study Intervention (prescription of Arm A or Arm B) note intervention is continued over the duration of follow up.			X				
Assessment of Serious Adverse Events*				X	X	X	X
Patient reported outcome measures	Asthma control test		X	X	X	X	
	CHU9D tool		X	X	X	X	

Schedule of Assessments:				Follow up schedule.			
Procedures		Screening	Baseline	4 months	8 months	12 months	4 weeks post study Completion
	Adherence questionnaire			X	X	X	
*adverse events and serious adverse events will be reported throughout the follow up period and for 4 weeks following the end of the intervention.							

Availability of patient reported questionnaires are described below:

PRO Set	Day questionnaire available	Initial email (days)	First reminder (days)	Second reminder (days)	Final reminder (days)	Questionnaire close (days)
Baseline	0*	0	14	28	42	104
4 Months (17 weeks)	105	105	119	133	147	223
8 Months (34 weeks)	224	224	238	252	266	349
12 Months (52 weeks)	350	350	364	378	392	398
*- 0 days = point of randomisation.						

Telephone discussion with parents:

Practices will review their list of potentially suitable patients and invite them to make contact with the practice if interested. The person's parent/legal guardian, may request a telephone call with a delegated member of the practice study team or central study team to discuss the trial and possible participation. The practice may contact the person's parent/legal guardian to follow-up interest if no response is received following the first invitation.

GP Visits:

Participants will need an appointment/contact with appropriately delegated practice study team member, or central study clinician, prior to randomisation, to confirm eligibility and for documentation of informed consent. This appointment may be by telephone, video call or an in-person clinic visit. Randomisation will take place as soon as possible following completion of informed consent/assent and information given to the participant on the intervention that they have been allocated. Participants will continue to have contact with their GP as and when needed as part of their standard care, but no further study specific GP appointments will be scheduled. Data on unscheduled GP visits, including face to face and remote, will be collected from the EHR.

Online assessments

At baseline, 4 months, 8 months and 12 months, patients, and/or the parent/legal guardian, will complete a series of PROMs via the IRSP. Parents/legal guardians will be encouraged to complete assessments with

younger children but older children may choose to complete the assessments themselves or with support from a parent.

The baseline PROMs will be available for 104 days after randomisation. PROMs at 4, 8 and 12 months will be available online for 119, 126 and 49 days respectively following the closure of the previous survey window. Participants will receive an email reminder that the PROM is available in REDCap. Reminder emails will be sent two, four and 6 weeks after the PRO has become available..

Asthma Control Test

For participants aged 6-11 years, there are seven questions. Questions 1-4 are completed by the patient with support from their parent/legal guardian. Questions 5-7 are completed by the parent. The questionnaire takes approximately five minutes to complete.

For participants aged 12 years and above, there are five questions completed by the trial participant. The questionnaire takes approximately one minute to complete.

CHU9D Tool

The CHU9D questionnaire will be completed by participants aged 6-16 years. There are nine questions with five response levels per question. The CHU9D takes approximately seven minutes to complete.

Adherence Questionnaire

The adherence questionnaire, based initially on the MIS-A, but revised to meet the objectives of as-needed ICS treatment, will be used to measure patient reported adherence. There are five questions completed by the trial participant and/or the parent/legal guardian. The modified adherence takes approximately five minutes to complete.

Confirmation of consent

Participants, assented as a minor, who reach the age of 16 years during their trial participation will be asked to provide their consent to continue participation.

The Investigator will be notified of any participants who reach the age of 16 and a short information sheet plus consent form will be sent to the participant by email/hard copy/link in SMS.

11.6.1 Efficacy Assessments

See section 9.2.

11.6.2 Safety Assessments

Principal Investigators will be responsible for reporting SAEs via eCRF on IRSP, within 24 hours of being informed of the event. Once the form is submitted by the site Principal Investigator, the Sponsor, CI and CPRD Monitors will receive an email with a PDF format of the SAE eCRF.

11.6.3 Health Economic Assessments

See section 9.2.

11.7 Participant incentives for PROM completion.

Trial participants and their parent/carer will complete PROMs at intervals described in the schedule of assessments. Completion of PROMs at each time point is expected to take around 20 minutes. In ASYMPTOMATIC, a non-inferiority trial, the completion of the PROMs, in particular the adherence questionnaire, is critically important.

To acknowledge the time taken to complete the PROMs and their importance, a £5 gift voucher will be offered to participants completing all of the PROMs at each time-point. A total of £20 will be available per participant if all PROs are completed at all four follow up time points.

Gift vouchers will be provided as a voucher code that can be used in multiple online/high street retailers and sent to the participants parent/carer by email after completion of PROMs at each time-point.

The £5 voucher will only be awarded if all PROMs at a particular follow up time point are completed in full.

Reports will be generated from the IRSP and REDCap systems on a biweekly basis to allow prompt issue of PROMs and facilitate delivery of the voucher following completion. However, participants will be advised that it may take up to 6-8 weeks following completion to receive their voucher.

11.8 Intervention Discontinuation and Participant Discontinuation/Withdrawal

In consenting to the trial, participants/ persons with parental responsibility agree to all trial activities including administration of the trial intervention and treatment and follow-up assessments and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate), the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal and the actions that should be taken

11.8.1 Premature Discontinuation of Trial Intervention

Participants may discontinue treatment for reasons including, but not limited to those listed below. Discontinuation of the trial treatment for reasons other than death do not require participant withdrawal unless this is requested by the participant.

- Participant-led i.e. request by the participant / person with parental responsibility / legal representative / consultee
- Unacceptable toxicity (see Section 12 for Adverse Event reporting)
- Intercurrent illness preventing further treatment.
- Pregnancy
- Death
- Clinician-led:
    - Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion.
    - Reasons of non-adherence or non-compliance with treatment or other trial procedures
    - Participant meets an exclusion criterion (either newly developed or not previously recognised)

Discontinuation from the study intervention does not mean discontinuation of the study altogether, and the remaining study procedures, follow up assessments and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn).

11.8.2 Participant Withdrawal from Follow Up

Persons with parental responsibility and patients aged 16 years and above are free to withdraw the participant from follow up at any time without providing a reason, but the reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses. The participant will not contribute further data to the study.

The PI at site, or delegated individual at site, will complete a Study Withdrawal form within the Treatment & Study Withdrawal section of the eCRF (IRSP) which will specify which type of withdrawal the patient is requesting.

The status of the patient will change to 'Withdrawn' on IRSP. CPRD Trial Monitors will have this information recorded on the Trial Monitoring dashboard IRSP and will act accordingly when providing the study data to the Sponsor.

Patients who have withdrawn or who have previously been considered eligible and declined consent, will remain in the practice screening list, which isreconciled against subsequent updates to the cohort search to ensure that they are not approached again.

If persons with parental responsibility/young people express a wish to withdraw from follow up, the research team at site should ascertain if this is for all elements of trial follow-up, or if for example data from the EHR can still be collected for the trial. In the case of ongoing adverse events, participants should be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable. Any SAEs will be notifiable to the CPRD via processes detailed in Section 12 even if a participant has withdrawn from follow up.

11.8.3 Participant Transfer

If the enrolled participant changes their Primary Care provider, the flow of electronic health record data to CPRD for that patient will cease. The original primary care provider records a 'registration end date' in the EHR which can be monitored by CPRD for enrolled participants, and any instances where this occurs will be reported to the TMG. The participant will be marked as 'withdrawn from treatment' on the 'Treatment and Study Withdrawal' eCRF form 1: Withdrawal from Randomised Treatment. Clinical management of the patient will continue as before under the new GP, who may decide to continue with the treatment regimen the patient was randomised to. The participant will continue to receive the patient reported outcome questionnaires by email unless they express a wish to withdraw from follow up IRSP. The regular collection of safety information from the EHR is only possible if the patient moves to a practice that is contributing data to CPRD, outcome measures from the linked datasets (Hospital and ONS) will still be extracted at the end of the trial.

As an additional check, enrolled participants will be asked at the 4, 8 and 12-month patient-reported outcome time points if they have moved to another Primary Care provider. This will be monitored as part of the overall trial monitoring plan.

11.8.4 Loss to Follow-up

Loss to follow-up should be minimized by the pragmatic design of this study, however, as described above if a participant moves from a CPRD contributing practice to a non-contributing practice, long-term follow-up of health outcomes will not be possible and the participant will be considered lost to follow-up.

Participants will be contacted at baseline and at 4 month intervals to complete the PROs in REDCap . Patients will have the opportunity to complete the PROs until the start of the next follow up time point. Data entered outside of these windows will be considered as missing.

In the event of treatment modification participants will continue to be followed up as planned.

11.9 End of Trial

The end of the trial is defined to be the date on which data collection for all participants is frozen and data entry privileges are withdrawn from the IRSP. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

Site and closure activities will be centrally coordinated and conducted in accordance with CPRD processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and the competent authority (MHRA).
- Quality Control checks of the Investigator Site Files and Trial Master File as appropriate.

11.9.1 Study Discontinuation

In the event of trial discontinuation participants, will revert to the standard care offered by the practice with which they are registered.

Post-trial Care

At the end of the 12-month study period the participant's GP will be informed and care will continue in line with current standard practice.

12 SUB-STUDIES/NESTED STUDIES

None

13 SAFETY REPORTING

13.1 Overview

ASYMPTOMATIC will employ a risk-adapted approach to adverse event reporting. The rationale for this is:

(1) Clinical events are captured from routine NHS care coding, meaning that events have already been identified and managed within the NHS.
(2) GPs across the UK are already experienced in the prescription and monitoring of patients taking asthma therapy.
(3) Drugs used as interventional therapy in this trial have an established safety profile in patients with asthma. The ASYMPTOMATIC trial is not expected to provide any new data related to the safety profiles of the drugs prescribed. Therefore, ASYMPTOMATIC will use a risk-adapted approach to safety reporting.
(4). Collection of HES outcomes will occur on a yearly basis (approximately).
(5) Asthma exacerbation, hospitalisation and death will not be reportable SAEs as they are nominated outcomes of the trial.

13.2 Definitions

Adverse Event (AE) - Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse Reaction (AR) - Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Causality - The assignment of the causality should be made using the definitions in the table below:

Table 2: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
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 participant's clinical condition, other concomitant treatment).
Possibly	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 participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

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

Events that are assessed as being possibly, probably or almost certainly related will be reported as having a reasonable possibility of being related, and events assessed as unrelated or unlikely will be reported as having no reasonable possibility of being related.

Assessment of causality should be made based on known safety profiles of SmPC and known risk profiles of other drugs in the same class. If any doubt about the causality exists, the local investigator should inform CPRD who will notify the Chief Investigator. In the case of discrepant views on causality between the treating investigator and others, the opinion of the treating investigator will never be downgraded, and the MHRA/REC will be informed of both points of view.

Expected - An event will be considered expected if it is listed within the current and approved reference safety information (RSI), based on section 4.8 of the SmPC, for the study at the time of the event's onset. The nature, severity, or frequency of the event should be considered – if this is consistent with that described for the type of event in the RSI, based on section 4.8 of the SmPC the event should be assessed as expected.

Reference Safety Information (RSI) - The information used for assessing whether an adverse reaction is expected. This is contained in the Summary of Product Characteristics (SmPC) for the product and must be approved for use by the MHRA. The RSI used to assess the expectedness of a SAR must be the current approved version at the time of onset of the SAR. The RSI for this trial is defined in section 4.8 of the SmPC.

Serious - A safety event / reaction is assessed as serious if it:

- Results in death;
- Is life threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE);
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis);
- Other important medical events (these may not result in death, be life-threatening, overdose, secondary malignancy or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

Serious Adverse Event (SAE) - Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR) - An adverse reaction which meets the definition of serious is a Serious Adverse Reaction. A Serious Adverse Reaction event that has been assessed as 'expected' according to the Reference Safety Information (see below) will remain classified as a Serious Adverse Reaction only, however some Serious Adverse Reactions that are considered 'unexpected' will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).

Suspected Unexpected Serious Adverse Reaction (SUSAR) - An adverse reaction that is classed in nature as serious and "unexpected" (i.e. not listed within the Reference Safety Information (RSI) approved for the trial by the MHRA and current at the time of onset of the SUSAR).

Unexpected - An event will be considered unexpected if it is not listed within the current and approved reference safety information (RSI), based on section 4.8 of the SmPC, for the study at the time of the event's onset. The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the RSI, based on section 4.8 of the SmPC the event should be assessed as unexpected.

13.3 Operational management of safety reporting

All safety events which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from routine monitoring of the participant's EHR by CPRD for a defined set of AE codes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. "serious" events are to be reported to CPRD via ISRP in an expedited manner). Any questions concerning adverse event reporting should be directed to the CPRD in the first instance.

Safety events (assessed as serious / related / expected) will be recorded on a Serious Adverse Event Form in IRSP; AEs and ARs will not be reported unless considered SAE or SUSAR. SAEs and SUSARs will be assessed for by the clinical co-chief investigator or their delegated medical cover.

The CPRD IRSP allows Investigators to directly input a potential SAE for any recruited participant. This entry is then automatically flagged to the Sponsor and to the CPRD team who will process the potential SAE, with expectedness determined by the Chief Investigator, Deputy Chief Investigator or delegate. Source data for the SAE form is controlled by the Investigator with no editing rights by CPRD, Sponsor or CI. Any amendments or updates by the Investigator lead to the creation of a new linked SAE form with a clear audit trail.

Specific outcomes will be collected from CPRD and will be matched against the IRSP reports on a yearly basis to create a summary for reporting to the IDSMC, TSC and MHRA. If SAEs are reported in IRSP or identified from within the EHR more often than expected the frequency of the automated safety reporting will be increased. The precise trigger points for this eventuality will be set by the IDSMC, and ratified by the TSC, but would be expected to be twice the rate observed in the SmPC.

Adverse reactions and Yellow Card reporting: As with any potential adverse reaction which occurs during standard care, Investigators will be encouraged to complete an MHRA Yellow Card submission. 'Yellow card' reports do not form part of trial data.

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.
When reporting "serious" safety events the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved
- resolved with sequelae (specifying with additional narrative)
- not resolved/ongoing
- ongoing at final follow-up
- fatal or unknown.

13.4 SUSAR Reporting

SUSAR reporting is unlikely in this trial and is not expected to occur at the same level as would be expected in other clinical trials. This is due to the high volume of safety data collected on this class of drugs, and their common use in NHS routine practice.

Data collection for the trial will be based wholly on NHS coded outcomes from both primary and secondary care. As such, it is not likely that further details of any SAE will be available to the central study team, and any action/outcomes may only be known at the next yearly data collation point. Although this limits the value of expedited reporting from either a safety or regulatory perspective, the processes in place still meet the Sponsor's legal obligations in terms of SUSAR reporting. PIs reporting SAEs via IRSP will be asked to note their opinion on causality and these will then be reviewed by the CI who will make a decision on the expectedness based on the RSI. If the event is considered to be a possible SUSAR it will be reported in line with the regulatory guidelines.
All SUSARs occurring from the time of randomisation until 30 days after the end of the treatment period must be recorded on the relevant form and sent to the Sponsor by the Chief Investigator or delegate within 7 days of the research staff becoming aware of the event. Any SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred until resolved. The sponsor, or their delegate, will inform the MHRA and REC within the required expedited reporting timescales.

For each SUSAR the following information will be collected:

- Full details in medical terms and case description (if applicable and known).
- Event duration (start and end dates, if applicable and known).
- Vital status of the patient (where known).
- Opinion on causality (i.e. relatedness to the trial treatment).
- Seriousness criteria.

- Confirmation that the event is unexpected.

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

In accordance with the terms of UK clinical trial authorisation, SUSARs which are fatal or life-threatening will be reported to the regulator as soon as possible and in any case no later than 7 days after the Sponsor (or delegate) is first aware of the event. If the initial report is incomplete, a complete report will be submitted within an additional 8 days. SUSARs that are not fatal or life-threatening will be reported within 15 days of the Sponsor (or delegate) first becoming aware of the event. Additionally, SUSARs will be reported to the trial Sponsor and Principal Investigators of participating sites within the agreed timelines.

13.5 Additional measures to support safety reporting

To guard against unreported events, ASYMPTOMATIC will operate additional measures to capture additional potential SAEs. CPRD receives daily data collections from General Practices, which are processed into a secure database. For participants recruited into ASYMPTOMATIC, this data will be made available for regular, frequent searches. Such searches will be used to identify key new events occurring in the patient's coded electronic health record, including potential SAEs such as admittance to hospital. Upon identification of such events, the Site PI will be notified by email and asked to record details of the potential SAE within the IRSP. This process will work in concert with the extraction of coded data within primary and secondary care and will feed into the safety reporting processes described above.

Additional events of interest may also be captured using the SAE form in IRSP. For example, exacerbation of asthma may be identified during the routine safety monitoring of the EHR and be reported through the IRSP.

13.6 Responsibilities

Investigator Reporting Responsibilities

The PI is responsible for ensuring that all safety events requiring recording on this study, which the local research team becomes aware of, are reported using IRSP. It is the responsibility of the PI/Co-PI as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events.

Safety events which meet the definition of "serious" must be reported in IRSP on an SAE form **as soon as the Investigator's site becomes aware of the SAE.** The SAE form should be completed by an appropriately delegated member of the research team. The assessments of seriousness and causality must be performed by an appropriately medically qualified person. Minimum reporting information must be provided in initial reports for all studies.

Note: In the absence of a delegated medically qualified person, the form should be completed by an alternative member of the research site trial team and submitted on IRSP. As soon as possible thereafter,

the responsible investigator should check the SAE page, make amendments as appropriate, sign and re-send to the CPRD. The initial report shall be followed by detailed follow-up reports as appropriate.

REPORTING AN INITIAL OR FOLLOW-UP SAE

The investigator should ensure the actions below are completed for all reportable SAEs:

1) A PDF of the SAE form will be sent via email to the CI, PI and Monitors automatically by the IRSP
2) The patient's name **should not** be used on any correspondence. The patient must be identified by trial number, age or month and year of birth and initials **only**.
3) SAEs must be subsequently followed up in line with the processes below:
    - Follow up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised (see Section 11.7.4). Note: Follow-up may continue after completion of protocol treatment if necessary.
    - Follow-up information is noted on the SAE form as soon as more information becomes available, the GP, CPRD and Sponsor will receive an email with the SAE revision.
4) Extra, annotated information and/or copies of anonymised test results may be provided separately.

BACKUP PROCESS

In the event of a problem with the IRSP (power failure, server failure etc.) SAEs should be reported by secure email of a completed trial specific SERIOUS ADVERSE EVENT FORM to studysupport@mhra.gov.uk.

PIs are encouraged to report drug-related events using the MHRA yellow card system.

CPRD Responsibilities

The trial Sponsor has delegated to CPRD the duty of onward reporting of safety events to REC and the Regulatory authority (MHRA). SOPs will be followed to ensure appropriate reporting as detailed below.

CPRD will be responsible for:

1. Configuring and maintaining IRSP to support the reporting of SAEs by Investigators and including establishing automatic notification in the form of a PDF copy of the report which will be sent to the Sponsor, CI and CPRD on submission of the SAE by the PI.
2. Ensuring all reported SAEs are forwarded to the CI, or Medical Reviewer/Clinical Coordinator within 24 hours of receipt (during business hours).
3. Ensuring that, where a CI confirms that the reported SAE is a SUSAR that all relevant information is reported to Sponsor so that Sponsor can submit the SUSAR to the MHRA in the mandated timelines. Following up reported SAEs with the Investigator until resolution or end of trial (as applicable).
4. Collaborating with the CI and Sponsor to submit the Annual Safety Report to REC and Development Safety Update Report (DSUR) to the MHRA on an annual basis.
5. Collating the information required to produce safety reports for the Chief Investigator, Sponsor and oversight committee(s) including provision of an annual data extract to support SAE analysis.

The PIs at all institutions participating in the trial will be notified of any SUSARs within a reasonable timeline.

Any concerns raised by the TSC/IDSMC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential to carry out site visits if there is suspicion of unreported SARs / SAEs in the patient's EHR. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

CI (or delegate)
The CI (or delegate) will review information provided by site and for all events assessed as "related" will provide an assessment of "expectedness". Safety events which are assessed as "serious", "related" and "unexpected" will be expedited to the MHRA as a SUSAR.

Sponsor
The Sponsor will retain overall responsibility for pharmacovigilance, accurate safety records and for ensuring accurate and timely safety reports. In this study some of these responsibilities will be delegated by the Sponsor to CPRD as detailed above.

Oversight Committees (IDSMC and TSC)
The IDSMC will be responsible for interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will provide a recommendation to the TSC concerning the continuation of the study.

14 STATISTICAL CONSIDERATIONS

14.1 Sample Size

Sample Size Calculation

Calculation of the required sample size and justification of the non-inferiority margin:

The non-inferiority margin was determined using the approach recommended by Food and Drug Administration (FDA) guidelines [36], referred to as the fixed margin method, which involves a combination of statistical and clinical considerations. The lower 95% confidence limit from a meta-analysis of all active control versus placebo trials provides a conservative estimate of the active control treatment effect (say M), a percentage of which it is deemed clinically important for the experimental treatment to preserve (say P). The remaining fraction (1-P)*M defines the maximum acceptable non-inferiority limit of experimental treatment compared to active control. The percentage is often set at 50% (48) i.e. the non-inferiority margin is half the lower CI limit of the established (active control-placebo) rate.

Two randomised trials have examined the proportion of children experiencing asthma attacks requiring OCS when randomised to daily ICS (active control in our study) versus placebo[22,37]. There is also one large study in adults and children but this is not relevant because asthma attacks were reported as a composite outcome of OCS or hospitalisation, and paediatric results were not reported separately[38]. Of the 1041 children in the Childhood Asthma Management Program trial, 311 were randomised to receive twice daily budesonide 200mcg and 418 received placebo [37]. Of 288 children in TREXA, 72 were randomised to receive maintenance ICS and 74 received placebo[22]. Synthesis of the percentage of children experiencing asthma attacks in these trials generates a mean percentage (of the absolute difference between daily ICS and placebo exacerbation rates) (95% CI) of 18.7% (12.2%, 25.3%). As such, our chosen non-inferiority margin (5%) is less than half of the lower 95% confidence limit for active control effect versus placebo (12.2%). This conservative fixed margin method is considered robust in protecting against the potential for bias or lack of reliability in the control arm effect estimate in non-inferiority studies (which can cause biased treatment effect)[39].

In a large population based cohort study of people with asthma, using the CPRD database, 10,807 of 59,92910807/59929 (18%) of children taking maintenance ICS without additional therapy (BTS Guidelines Step 1 and 2[7]) had an asthma attack requiring OCS[35], with a median follow up of 3.3 years. As these observational data suggest that the exacerbation rate within 12 months may be less than 18% but are less reliable than the randomised evidence, 18% is taken as the estimate of the 12 month exacerbation rate, likely over-estimating the sample size needed for this non-inferiority trial. Assuming, therefore, that the expected proportion of children in each group who have an asthma attack requiring OCS will be 0.18 and using an equivalence margin of 0.05, **a total sample size of 1854 (927 per group) will provide 80% power with a one-sided 2.5% significance level to reject the null hypothesis that the new regime is inferior to the standard regimes.**

We will check our exacerbation rate estimate in Stage 3 of the internal pilot (by calculating the pooled exacerbation rate after 100 participants have been followed up for 12 months) and inflate the sample size accordingly, if the pooled estimate exceeds our estimate of 18%. However, as the Bloom data suggest that the 12 month exacerbation rate may be less than 18% (possibly in the region of 10-12%) which would in fact

lead to a reduction in sample size, we will not reduce the target sample size from the original estimate. Instead, we will determine the likely increase in power of the study if the observed 12 month exacerbation rate is less than we have (conservatively) estimated, with the hope that the power of the trial could in fact be in the region of 90%.

Given that the primary outcome of asthma attacks requiring OCS is to be extracted from routine data in EHR, the only sources of attrition will be when patients move to a non-CPRD registered GP practice during their 12 month follow up period, or if any patients withdraw consent for their follow up data to be included in analysis. CPRD data suggest that a maximum of 4% of patients move to a non-CPRD registered practice during a 12 month period, and previous experience of paediatric LCTC trials suggests that complete withdrawal by patients is rare. As such, we will inflate the sample size to 1932 (966 per group) to allow for up to 4% loss to follow up. Observed retention rates will be assessed as part of Stage 2 of the internal pilot, and the IDSMC will continue to monitor retention on an annual basis. If attrition is observed to be >4%, the recruitment target will be increased to allow for the observed attrition rate.

As sample size calculations are intended to provide ballpark (rather than exact) recruitment targets, we will aim to recruit approximately 2000 patients (1000 per group).

Feasibility of Sample Size

The estimated study duration is 54 months, including 6-months set up time before the trial opens to recruitment (during which we will conduct necessary regulatory steps, recruit team members, and set up the study), 30 months for recruitment, 12 months for follow up and 6 months at the end for final analysis/reporting. CPRD figures estimate an average of 27 (incident or prevalent based on 16,606 from 614 sites) and 5.3 (incident based on 3,004 from 562 sites) asthmatic children meeting our eligibility criteria per practice per year. With a consent rate of 40% (as we observed in a previous trial of asthma treatment in primary care [40], each practice should expect to recruit 10 or 11 patients in the first year and 2 or 3 patients in subsequent years. Allowing for staggered site opening, it is assumed that on average sites will recruit for a total of two years i.e. approximately 13 patients in total. The recruitment target of 2000 will therefore require approximately 155 recruiting practices. We will cost for 250 practices, to allow flexibility in case the internal pilot highlights lower than expected consent/eligibility rates (for example, a certain percentage of these children will be on additional treatments which will render them ineligible). This number of sites is feasible given that CPRD have access to 1200 practices in England alone.

14.2 Method of Randomisation

Allocation Sequence Generation

The responsibility to deliver the randomisation process for this study will be delegated to CPRD. The randomisation schedule will be approved by the Sponsor (TMG) prior to configuration into IRSP. The randomisation schedule will consider:

- The number of treatment arms (two)
- The proportion of patients to be assigned to each treatment group (50%)
- The blocking structures, which will be randomly varied

The randomisation schedule will be produced using Stata® 15.1 (StataCorp LP, Texas),), it will be reproducible and a master copy of the randomisation schedule plan (excluding exact block sizes/randomisation code to maintain allocation concealment) will be kept in the trial master file. The randomisation code, log file and allocation list (randomisation schedule) will be stored securely at CPRD and will not be accessible to those outside of the CPRD Interventional Research team.

14.2.1 Concealment and Implementation of Allocation Sequence

Patient allocations will be irrevocably generated after completion of the web-based randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial.

14.3 Interim Analyses

Descriptive summaries of the accumulating data will be presented at regular intervals (at least annually) for review by an IDSMC. These summaries will be prepared at the LCTC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of clinicians including those taking part in the trial and the general clinical community.

A formal interim analysis will be carried out when half of the total sample size has been followed up for 12 months. The trial will be stopped early for lack of non-inferiority if the one-sided p-value for non-inferiority of the primary outcome is >0.5 and will continue otherwise (providing that there are no other reasons to stop). This analysis will provide a 50% chance of early stopping if the new treatment regime is truly inferior, as defined by the non-inferiority margin, and will reduce power minimally (by approximately 0.5%) if the new treatment is non-inferior to the standard treatment regime.

14.4 Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the SAP are summarised here. Analyses will be conducted using the intention to treat principle with two-sided 95% confidence intervals and 5% level of statistical significance

(with the exception of the primary outcome, for which inference regarding non-inferiority will be assessed using a one-sided 97.5% confidence interval and 2.5% level of statistical significance). The primary outcome, and other binary outcomes, will be analysed using logistic regression. As a subgroup analysis we will investigate differences between groups based on age, socioeconomic status and atopic conditions.

As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the SAP.

Internal pilot:

A 3-stage internal pilot is incorporated into the study.

- Stage 1 (6 months after first site opening): feasibility of site opening and recruitment
- Stage 2 (12 months after first randomisation): recruitment, retention, adherence and ACT reporting rate
- Stage 3 (once 100 patients have reached 12 months follow up): pooled exacerbation rate

The following rules will apply for each criterion:

- Go threshold reached: proceed with trial
- Amend threshold reached: discuss with Trial Steering Committee (TSC) and Independent Data Safety Monitoring Committee (IDSMC) and implement amendments to trial conduct to increase site opening, recruitment and/or outcome completion rate
- Stop threshold reached: prepare and discuss with TSC and IDSMC a detailed plan of how the trial can be amended; if not considered acceptable, a recommendation will be made by the TSC/IDSMC that the trial should close.

Stage 1 (assessed at 6 months):

At 6 months (from first site opening), site opening and patient recruitment will be assessed:

Progression Criteria	Go	Amend	Stop
Sites open	>50 sites	25-50 sites	<25 sites
Open site recruitment rate per 6 months	>1 participant	0.5-1.0 participants	<0.5 participant

Stage 2 (assessed at 12 months):

At 12 months (following first randomisation), recruitment, adherence and ACT reporting will be monitored:

Progression Criteria	Go	Amend	Stop
Adherence questionnaire completion rate	>80%	40-80%	<40%
Asthma Control Test completion rate	>80%	40-80%	<40%
Sites open	>100 sites	50-100 sites	<50 sites

Retention will also be assessed at Stage 2, based on all responses to the ISRP questionnaire (asking patients about whether they moved GP practice) received from patients at 4, 8 and 12 month follow up, as well as any withdrawals of consent from patients who do not want their follow up data to be included in analysis. If attrition is observed to be >4%, the recruitment target will be increased to allow for the observed attrition rate.

Stage 3 (assessed once 100 patients have reached 12 months follow up):

The pooled exacerbation rate after 12 months follow-up will be calculated once 100 patients have been followed for 12 months. If the pooled estimate varies from our estimate of 18%, the sample size or power of the trial will be inflated accordingly.

Guarding against false conclusions of non-inferiority in our study:

Non-differential misclassification: Asthma should be diagnosed if a clinical history is supported by physiological tests. However, there is neither a gold standard for how the clinical presentation, nor the physiological tests, should be interpreted. Clinical prediction models are not recommended (56), and national guidelines within the UK vary in their recommendations[41]. One retrospective Dutch study suggested that 53% of children with asthma in primary care may be over-diagnosed[42], and a recent UK study in primary care suggested that in 15% of children with asthma this diagnosis is inaccurate [43]. We see no reason why over-diagnosis of asthma should be higher in one arm of the trial than the other, but it may bias the results towards non-inferiority. To minimise the risk of misclassification, we will only include children with a prescription of an asthma medication. We will also undertake an accompanying sensitivity analysis in those children in whom there is some further objective or supporting evidence for a diagnosis of asthma. This includes children who at time of diagnosis have a documented test showing airway obstruction (reversibility on spirometry, variable peak expiratory flow rate) or inflammation (raised Fractional Exhaled Nitric Oxide >30 parts per million), or who by the end of the treatment period have ever a coded attendance for another atopic condition (eczema or hay fever), or prescription of antihistamine, topical corticosteroid, or emollient to treat these problems.

Treatment switching: Given that poor study conduct quality (including eligibility violations, poor adherence, treatment crossovers and missing data) typically leads to a dilution of the treatment effect, and thus an increased probability of falsely concluding non-inferiority, we will supplement intention to treat analyses with appropriate causal methods to adjust for treatment crossovers rather than rely on per protocol or as treated analyses (which are typically subject to selection biases). We will facilitate such analyses by adding a question to IRSP (at the start of the adherence questionnaire) asking patients whether (and if so, when) they switched from their assigned treatment regimen to the alternative (i.e. patients in the maintenance ICS group switching to the symptom-driven ICS regimen or vice versa). Patients' adherence will also be assessed objectively from prescription and/or dispensing data, which will be summarised into continuous multiple-interval measures of medication availability/gaps (CMA). We will perform sensitivity analyses to explore these causal effects based on these adherence metrics.

Health Economics Analysis

A full health economic analysis plan (HEAP) will be written prior to the conduct of any comparative analysis of the treatment arms. The main features of the HEAP are summarised here. The economic analysis, adopting the perspective of the NHS, will be conducted to estimate the cost-effectiveness of symptom-driven versus maintenance ICS. Resource use will be estimated from data available from CPRD on the number and type of primary and secondary care (Hospital Episode Statistics) medical contacts, medicines prescribed and dispensed. Unit cost data will be obtained from routine hospital data (NHS reference costs) and other resources including the British National Formulary and Curtis' unit costs of health and social care. The primary economic outcome will be the incremental cost per QALY gained, estimated from responses to the CHU9D and applying UK preference weights[44]. The number of QALYs experienced by each patient will be calculated as the area under the curve, using the trapezoidal rule. A secondary analysis will assess disutilities associated with exacerbations that require oral corticosteroids in either the GP practice or Emergency Department, and hospitalisations, identified from the literature[45], and subtracted from patients' background utility values. Costs and benefits occurring after the first year will be discounted at 3.5% per annum. Total costs and QALYs will be used to calculate the incremental cost-effectiveness ratio of symptom-driven ICS. Where appropriate, missing resource use or health outcome data will be imputed. Non-parametric bootstrapped 95% confidence intervals for items of resource use, costs and QALYs will be estimated (10,000 replicates). We will also employ simple parametric approaches for analysing cost and QALY data that assume normal distributions given the large samples where the near-normality of sample means is approximated. Should the data indicate otherwise, we will develop a generalized linear model, to deal with problems such as skewness. A decision analytic model will be specified that takes into consideration any costs and health impacts of long-term adverse effects of ICS and OCS. Stratified cost-effectiveness analyses will be conducted based on age, and whether children are treated for atopic conditions. Estimates of ICERs will be compared with the NICE £20,000 to £30,000 per QALY threshold of cost-effectiveness (either in the NE or SW quadrants of the cost-effectiveness plane), and a range of one-way sensitivity analyses will be conducted to assess robustness of the analysis. Multivariate sensitivity analyses will be applied where interaction effects are suspected, and the joint uncertainty in costs and benefits will be considered through application of bootstrapping and estimation of cost-effectiveness acceptability curves.

15 DATA MANAGEMENT AND TRIAL MONITORING

For the ASYMPTOMATIC trial the responsibilities for Data Management and Monitoring are delegated to CPRD. A separate Trial Monitoring Plan will provide detail regarding the internal processes that will be conducted at the CPRD throughout the trial. Justification for the level of monitoring is provided within the Trial Monitoring Plan and the trial-specific risk assessment. All data will be managed as per local CPRD processes and in line with all relevant regulatory, ethical and legal obligations.

15.1 Source Documents

Protocol defined data will be captured using coded EHR recorded on CPRD database and associated health data sets available to CPRD from NHS Digital (referred to as linked datasets). An ASYMPTOMATIC source document list will be included in the data management plan and provide detail of what constitutes ASYMPTOMATIC-specific source data.

Data entered directly into the IRSP by patients/patient representatives will be considered the source data.

Dates of informed consent (plus assent where appropriate and if obtained) processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

15.2 Data Collection Methods

EHR data will be collected directly through the CPRD system, and so there is no requirement for Investigators or front-line NHS staff in Primary Care to complete case report forms to record demography and patient characteristics. This includes medical history, medications, clinical measurements and tests, and blood results. The Statistical Analysis Plan will detail each variable collected and relevant descriptions/determinants.

No follow-up visits are required as data linkage will occur through CPRD of primary care data, secondary care data (via HES) and data from the Office for National Statistics (ONS). Efficacy and safety outcomes will be collated from these sources based on a pre-specified clinical code set supplemented, where required, with a safety reporting process via IRSP. The code lists will be published and made available via Health Data Research UK (HDRUK). No trial-specific physical patient follow-up is required. PRO and adherence responses will be collected via IRSP, following notification by email to consenting individuals.

15.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities (section 5).

15.3.1 Central Monitoring

- A Trial Monitoring Plan will be developed and agreed by the Trial Management Group based on the trial risk assessment. Monitoring will be kept to the minimum needed to ensure compliance and patient safety, relating to participant enrolment, consent, eligibility, allocation and reporting of harm.
- Risk adapted trial monitoring will be carried out centrally and remotely via the CPRD IRSP based on an ongoing risk assessment process.
- Central monitoring in the trial will be carried out through the IRSP and includes monitoring of recruitment, electronic case report form completion of SAEs, protocol deviations, and reportable outcomes.
- Central site and recruitment monitoring will be undertaken via trial specific dashboards on IRSP.
- Site visits will only be carried out where ‘for cause’ criteria are triggered (as defined in the Trial Monitoring Plan) but may include: (1) Quality concerns at site following central monitoring checks; (2) Identification of a potential risk to the trial; (3) Investigation into a potential serious breach of the trial protocol/GCP; and (4) Other reasons as recommended by the Sponsor.
- Monitoring will be carried out by the CPRD study team who operate independently from the Sponsor and Principal Investigators. Where a triggered on-site monitoring visit is required, this will be carried out by CPRD staff. Monitoring reports will be compiled for each oversight committee as required.

Site monitoring visits may be ‘triggered’ in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

We will address possible contamination between treatment groups through both communication and monitoring strategies:

Communication:

(i) The participant information sheet will explain the importance of the trial, adherence and completion of data through IRSP.

(ii) We will maintain communication with GPs through a study newsletter which will update them about study recruitment and highlight any issues needing attention such as adherence.

Monitoring:

(i) The ordering of repeat medication through the prescription generating and issuing channels is likely to vary between practices and certainly between England and Wales, where GPs do not have electronic issue EPS direct to pharmacies. However, all four GPs with whom we discussed using either EMIS or Vision systems agreed that early requests would be detected.

15.3.2 Clinical Site Monitoring

There will be no planned clinical site monitoring visits.

Risk Assessment

A trial risk assessment will be undertaken by the Sponsor prior to trial opening.

Confidentiality/Data security at CPRD

The CPRD platform enables secure screening of patients for recruitment and does not require sharing of any patient identifiers outside the practice. Data processing is conducted on a locked-down suite of servers with no external internet capabilities and yearly penetration tests.

The CPRD IRSP system is cloud-hosted in Azure, operated by Microsoft. The data centres have climate control, redundant power (including generators), redundant connectivity, fire suppression and strict physical access controls. All visits must be pre-booked by identified individuals after providing a valid business justification for the visit, such as compliance or auditing purposes. All requests are approved on a need-to-access basis by Microsoft employees; photo ID must be presented, and records of this are maintained by the datacentre. Once within the facility, an individual's movements are controlled by two-factor authentication with biometrics and video cameras. To access the Datacentre floor, an individual must pass through full body metal detection screening and all server racks have front and back video camera monitoring.

Application and database administration are handled by the CPRD Heath Data Science (HDS) team in collaboration with DCSL as service contractors for CPRD/MHRA. Infrastructure administration is handled by NTT Data, as service contractors for CPRD/MHRA. Access to the virtual servers is via a Bastion connection, through the Azure Portal, with access controlled through Azure Active Directory. User access to the IRSP environment is managed by the CPRD Interventional Research team. Access is granted based on the user's role (either within the Team, or as Study Investigators or patient end-users).

The CPRD Security Level System Policy is in place that define the policies and procedures for data access, external data transfer etc. A full list is defined in the trial Data Management Plan.

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial

(e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms, and assent where appropriate, being supplied to the CPRD by recruiting sites. This transfer of identifiable data is disclosed in the PIS and consent form.

N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The trial Sponsor will preserve the confidentiality of participants taking part in the study. The Sponsor is registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified other members of the study team will be notified promptly to the trial Sponsor.

15.4 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will complete protocol training via IRSP prior to the start of any trial specific activity.
- The minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated will consist of a Principal Investigator and a co-Investigator at each site.
- The TC at the CPRD will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at CPRD and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

15.5 Records Retention

The retention period for the ASYMPTOMATIC data and information is 15 years from the official End of Trial date (defined in section 10.9).

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by GCP principles), including the Investigator Site File and the applicable participant medical records, for the full length of the trial's retention period and will arrange for confidential destruction at the end of this period as instructed by the sponsor.

The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties.

The Sponsor undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

16 REGULATORY AND ETHICAL CONSIDERATIONS

16.1 Statement of Compliance

This trial will adhere to the Medicines for human Use (Clinical Trials) Regulations 2004, principles of GCP and the principles of the World Medical Association Declaration of Helsinki, 1996.

The trial may involve the use of a UK authorised, medical spacer device which would be use for the intended purpose. Therefore this trial is not within the remit of the Medical Devices Regulation.

16.2 Ethical Considerations

Patients will be randomised and should be comfortable with either treatment arm prior to consenting to take part. Participants will not be able to choose their own treatment and those wishing to receive standard care will not be eligible to take part and will continue on their usual care pathway.

Whilst there are no study specific visits patients, will be required to complete patient reported outcomes measures using IRSP. Access to their GP will not be affected during the study and participants should contact their GP as needed.

Informed consent in a paediatric population

People with parental responsibility

The ASYMPTOMATIC trial includes participants under 16 years of age. The person with parental responsibility will be invited to discuss the trial with their GP or delegated trial personnel and to have any questions they have answered. The person with parental responsibility will be provided with a participant information sheet by email (or in hard copy at the discretion of their GP) and will be made aware of their right to withdraw from the trial at any time without this affecting their or their child's care/treatment.

Children and young people aged 6-15 years

Age-appropriate information will be provided and children encouraged to discuss the trial with their parents and to ask questions during the discussion with the GP. The age-appropriate information will include information about the risks and benefits of taking part. Assent will be sought as described in section 10.2

Young people aged 16 years.

If a young person reaches the age of 16 years during the treatment/follow-up period, they will be provided with an information sheet summarising the study and the reason for consent and then asked to consent and confirm their continued participation in the trial.

16.3 Approvals

The protocol, PIS, consent form and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA), Health Research Authority (HRA) and host institution(s) for written approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

16.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and relevant regulatory and ethical requirements (e.g. MHRA and REC) are handled based on their nature and severity.

16.4.1 Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and CPRD procedures as appropriate. They will be reported to trial oversight committees.

16.4.2 Serious breaches

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the CPRD who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as 'serious' will be reported as required by the regulations within 7 days by CPRD on behalf of Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, MHRA, or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

17 INDEMNITY

Alder Hey Children's NHS Foundation Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to participants treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

The treating GP practice continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the GP Practice's duty of care, or any negligence of the part of GP Practice employees. In these cases, clinical negligence indemnification will rest with the Clinical Negligence Scheme for General Practice (CNSGP).

The CNSGP covers practices for clinical negligence in conducting research with NHS patients in England, by way of care, diagnosis or treatment under one of the standard NHS primary care contracts, on or after 1 April 2019. All practice staff providing NHS primary care medical services including locums, nurses, students and trainees are covered for clinical negligence under CNSGP when undertaking the research activities as specified above.

18 PUBLICATION AND DISSEMINATION

18.1 Publication Policy

The results from all participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of TMG members and if there are named authors these should include the trial's Chief Investigator(s), Statistician(s), Health Economist(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship), then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC will be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

18.1.1 Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the ASYMPTOMATIC Consortium which will also be named at the manuscript head.

18.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the MHRA and REC. The results of ASYMPTOMATIC will be published regardless of the magnitude or direction of effect.

Trial participants will be able to access a plain language summary of the trial results via the study website and participating GPs will be notified that this is available.

18.3 Data Sharing

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers. All requests for access to the IPD should be addressed to the Sponsor and will need to specify how it is planned to be used. Requests will be reviewed by a committee comprised of the Chief Investigators, and representatives of the Sponsor, CPRD and LCTU.

19 CHRONOLOGY OF PROTOCOL AMENDMENTS

19.1 Version 2.0 (17-08-2021)

Original Approved version

19.2 Version 3.0 (10-01-22) – Substantial Amendment

Summary – Addition of information relating to voucher payment for PROM completion.

Page number	Description of amendment
1	Addition of ISRCTN number
11-12	EPS and PROM added to the glossary
13,14,	Sample size amended to 2000, 1000 per randomised group
27	Added secondary outcome “time to first asthma attack requiring treatment with OCS, clarification of 12 month treatment period
28	Updated to reflect practices in England only and process of site selection.
30	Co-enrolment section amended to delete “at the time of writing this protocol there are no actively recruiting trials…” PRW added as Co-CI
34	Reference to ICS information sheet deleted as this would not be used in routine practice.
35-36	Information added on data that will be accessed in relation to participant prescriptions.
38	Clarification added to outcome “asthma attacks requiring OC in GP or hospital setting”.
41	Figure 4 updated to include use of AccuRx and also process for non-consent.
42	Addition information provided for site training and patient list review.
44	Clarification that a consent form will be sent to participants with the information sheet.
46	Treatment allocation recorded in IRSP and the EHR.
47	Detail added for the randomisation process “The sequence of treatments will be randomly permuted in blocks of several randomly varying sizes.”
47	Process for staff getting an IRSP log in clarified
48-49	Schedule of follow up time window amended -2/+4 weeks Clarification of tasks in the table. Clarification of AE collection timeline
49	Process of telephone discussion with parents updated.
50	Section 11.7 added to describe participant incentives for PRO completion.
52-53	Participant transfer process updated.
54	Participant transfer pathway (figure 5) removed.
55	Follow up window clarified.
67	Reference to QoL score analysis deleted.
Throughout	Typos, abbreviations, punctuation, and formatting plus minor clarification of text.

19.3 Version 4.0 (05-10-23)

Summary – Amendment to include consent and PROM completion using REDCap plus a process to document telephone consent. Also addition of a central study contact number and expression of interest form as part of the recruitment process.

Page number	Amendment
3 and 8	Change of Sponsor contact/authorisation
12	Addition of REDCap
13 and 20	ICS spelled in full
29	Removal of need for unique email address
31	Clarification of process for translation/use of an interpreter
33	Clarification that ICS inhalers are recorded
34	Details updated on how children should take their inhalers depending on which arm they are randomised to
35	Clarification on the availability of linked data
41	Figure 4 updated
43	Invitation to include an expression of interest form
44	Addition of telephone consent including reference to appendix 1
44/45/46	Details of expression of interest form Details of the consent discussion and options for consent completion and documentation
51/52	Details of PRO availability timelines
64	Clarification of SUSAR reporting process
68	Details of randomisation schedule added
Throughout	Amendment of IRSP to REDCap for provision of PROs Amendment of typos and minor changes to improve clarity

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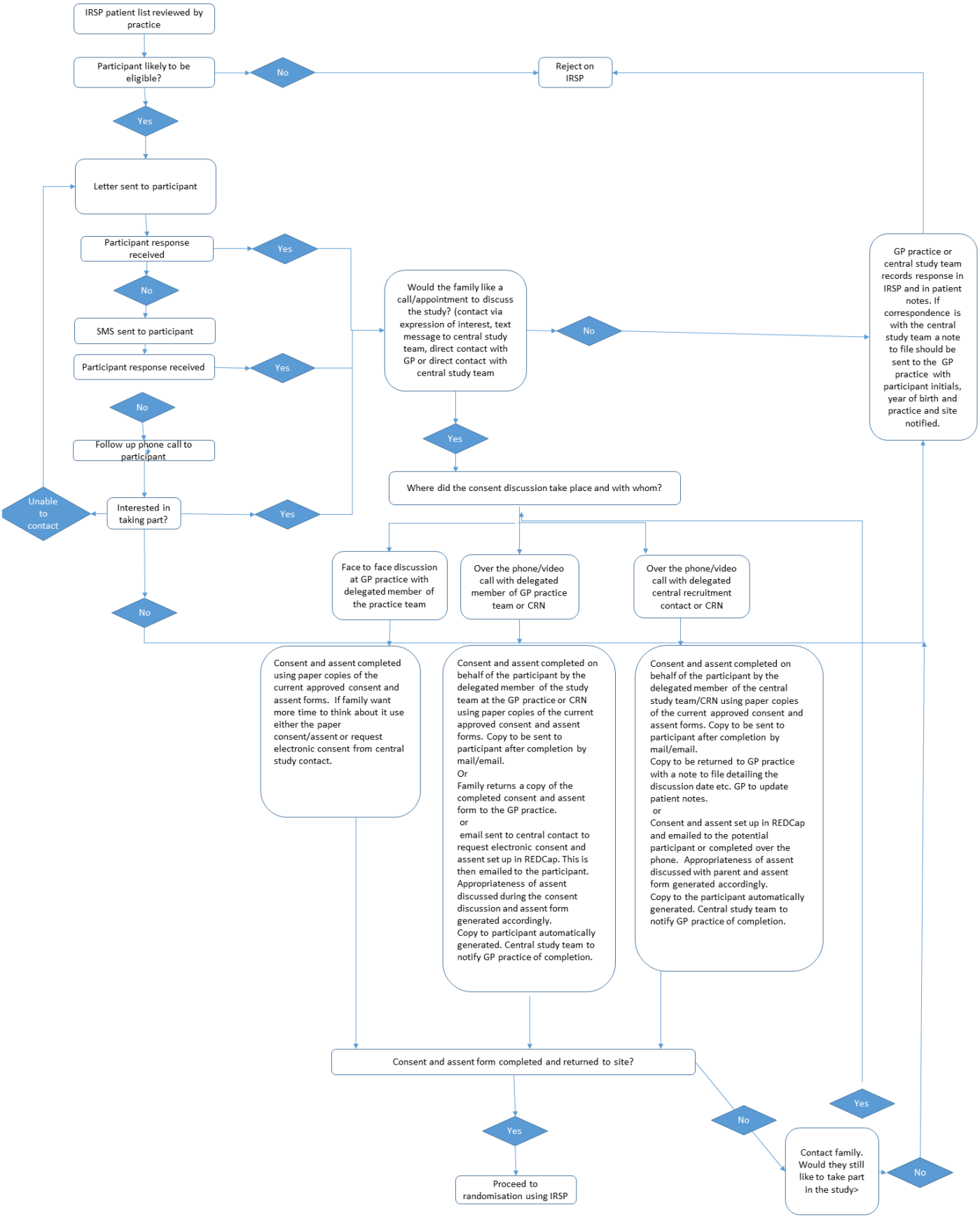
21 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to CA and / or Ethical review are submitted as separate version controlled documents.

22 Appendix 1


IRSP patient list reviewed by practice
Participant likely to be eligible?
No
Reject on IRSP
Yes
Letter sent to participant
Participant response received
Yes
No
SMS sent to participant
Participant response received
Yes
No
Follow up phone call to participant
Unable to contact
Interested in taking part?
Yes
No
Would the family like a call/appointment to discuss the study? (contact via expression of interest, text message to central study team, direct contact with GP or direct contact with central study team
No
GP practice or central study team records response in IRSP and in patient notes. If correspondence is with the central study team a note to file should be sent to the GP practice with participant initials, year of birth and practice and site notified.
Yes
Where did the consent discussion take place and with whom?
Face to face discussion at GP practice with delegated member of the practice team
Over the phone/video call with delegated member of GP practice team or CRN
Over the phone/video call with delegated central recruitment contact or CRN
Consent and assent completed using paper copies of the current approved consent and assent forms. If family want more time to think about it use either the paper consent/assent or request electronic consent from central study contact.
Consent and assent completed on behalf of the participant by the delegated member of the study team at the GP practice or CRN using paper copies of the current approved consent and assent forms. Copy to be sent to participant after completion by mail/email.
Or
Family returns a copy of the completed consent and assent form to the GP practice.
or
email sent to central contact to request electronic consent and assent set up in REDCap. This is then emailed to the participant. Appropriateness of assent discussed during the consent discussion and assent form generated accordingly.
Copy to participant automatically generated. Central study team to notify GP practice of completion.
Consent and assent completed on behalf of the participant by the delegated member of the central study team/CRN using paper copies of the current approved consent and assent forms. Copy to be sent to participant after completion by mail/email.
Copy to be returned to GP practice with a note to file detailing the discussion date etc. GP to update patient notes.
or
Consent and assent set up in REDCap and emailed to the potential participant or completed over the phone. Appropriateness of assent discussed with parent and assent form generated accordingly.
Copy to the participant automatically generated. Central study team to notify GP practice of completion.
Consent and assent form completed and returned to site?
Yes
Proceed to randomisation using IRSP
No
Contact family. Would they still like to take part in the study>
Yes
No