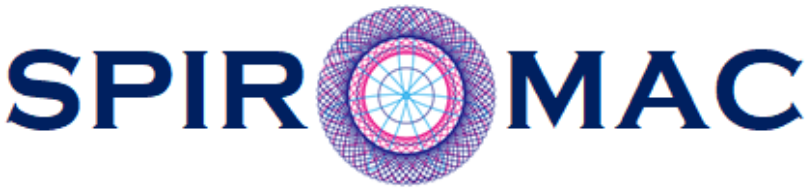

SPIROMAC
SPIROmetry to Manage Asthma in Children

PROTOCOL

A UK Collaborative Trial funded by the
NIHR/MRC Efficacy and Mechanisms Evaluation (EME) Programme

This Protocol has regard for the HRA guidance and order of content.

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Name:	Efficacy and Mechanisms Evaluation
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Other

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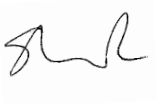
Signatures

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigators agree to conduct the trial in compliance with the approved, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Steve Turner, CI: 

Date: 07/10/2022

Lorna Aucott, Statistician: 

Date: 07/10/2022

Sponsor representative 

Date: 07/10/2022

Version history

Amendment no.	Protocol version no.	Description of changes (*incl. author(s) of changes*)	Date of protocol
	Version 1	New Document (based on version 3 of the CHaRT non-CTIMP protocol)	16 March 2022
	Version 2	Document revised as part of REC provisional opinion	09 May 2022
AM 03	Version 3	Revision to typographical error on funder end date (page 2) Update to information about who can undertake spirometry testing Remove reference to SAP in the information about stop-go criteria Update to footnotes 4 and 5 on the treatment step table and update to BTS step for drug numbers 18, 90 and 94 (Appendix 1)	29 August 2022

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Trial summary

TRIAL TITLE	SPIROmetry to Manage Asthma in Children
Short title	SPIROMAC
Rationale	Clinicians are uncertain of the role of spirometry in guiding asthma treatment in children, and this means that spirometry is used inconsistently across UK asthma clinics. Spirometry is recommended in some (but not all) guidelines as part of monitoring children with asthma, but the guidelines do not say how treatment should change in the context of changing spirometry result. SPIROMAC will be the first study to rigorously evaluate how spirometry can be used to guide asthma treatment and reduce the risk for asthma attacks in children.
Trial design	Two arm randomised controlled trial, with 1:1 randomisation to asthma treatment guided by spirometry plus asthma control (symptoms) or asthma treatment guided by asthma control (symptoms) only.
Eligibility criteria	***Inclusion criteria:*** • Aged 6-15 years • Asthma diagnosis confirmed by a doctor or a respiratory/asthma specialist nurse (or Read code for asthma if recruited in primary care) • patient/parent reported-asthma attack treated with at least one course of oral corticosteroids in the 12 months prior to recruitment • Be able to perform spirometry • Be able to understand written/spoken English. ***Exclusion criteria:*** • Not being able to perform spirometry satisfactorily • Presence of another chronic respiratory condition (e.g. cystic fibrosis) • Current treatment with maintenance oral steroids and biologicals (we cannot provide standardised step up/down treatment options)
Interventions	Intervention arm: asthma treatment guided by spirometry plus asthma control (symptoms) Standard care arm: asthma treatment guided by asthma control (symptoms) only
Randomisation and blinding	Eligible and consenting participants are randomised to the intervention arm or standard care arm. Random allocation will use a minimisation algorithm including a random element. The allocation will be blinded to the staff at site and to the participants.
Planned sample size	The total sample size is 550. With 275 children in each arm, we will have 90% power (with 5% significance, 2-sided) to detect a 28% reduced risk for asthma attacks, allowing for 5% of participants having incomplete primary outcome data.

Duration of trial	48 months; including 6 month set-up, 24 month recruitment, 12 month follow-up, and 6 months analysis, write-up and close-down.	
	Objectives	Outcome measures
Primary	**Efficacy:** To determine the efficacy of treatment guided by spirometry plus asthma control (symptoms) compared to treatment guided by asthma control (symptoms) alone in children with respect to asthma attacks up to 12 months post randomisation.	• Participant reported asthma attacks that require treatment with 1-7 days oral corticosteroids and/or intravenous corticosteroids
Secondary	**Efficacy:** To determine the efficacy of treatment guided by spirometry plus asthma control (symptoms) compared to treatment guided by asthma control (symptoms) alone in children with respect to: • any asthma attack • time to first asthma attack • health-related quality of life • Asthma control (symptoms) • Adverse events • Dose of inhaled corticosteroids	 • Participant reported asthma attacks • Participant reported first asthma attack • Paediatric Asthma QoL Questionnaire • Asthma Control Test/Children's Asthma Control Test • Participant reported event • Participant reported dose of inhaled corticosteroid
	Mechanism: To determine how treatment guided by spirometry plus asthma control (symptoms) (compared to treatment guided by asthma control (symptoms) only) leads to improved air flow (FEV1), lung volume (FVC) and reduced eosinophilic airway inflammation (Fractional Exhaled Nitric Oxide, FeNO) and is associated with reduced attacks.	• Spirometry • Fractional Exhaled Nitric Oxide
Statistical methods	The primary outcome will be analysed using negative binomial regression. The model will adjust for covariates and time in the study as the exposure. Secondary outcomes will be analysed in a similar manner using generalized linear models and the appropriate link function. The participants will be analysed as randomised. We will use casual mediation analysis to explore the indirect effects of treatment mediated by increase in spirometry as measured by FEV_1, FVC or a reduction in eosinophilic airway inflammation as measured by FeNO.	

Co-ordination	Local: by local respiratory and research teams Central: by Trial Office in Aberdeen (Telephone 01224 438089). Overall: by the Project Management Group and overseen by the Trial Steering Committee and the Data Monitoring Committee.

Lay summary

Asthma affects 1.1 million children in the UK. Asthma attacks are frightening for the child and their family, and can be fatal. A child has an asthma attack every 2.5 minutes, and one-in-10 of these children is admitted to hospital. Current guidelines say that recent asthma control (symptoms) should guide treatment choices to prevent attacks. What is needed is a reliable and evidence-based test, which can be used alongside asthma control (symptoms) to guide treatment and reduce the number of asthma attacks.

Spirometry is a simple breathing test which does not change over time when asthma is controlled. Spirometry could be a very useful test to monitor asthma because it measures lung function, i.e. how the lungs are working. To do spirometry children take a big breath in and breathe out through a tube as hard as they can. The amount of air they can breathe out in the first second is called the FEV1 (forced expiratory volume in 1 second). Currently, doctors disagree about how to best use spirometry to monitor asthma because of a lack of research evidence and conflicting guidance from experts. We know that only ~25% of hospital doctors in the UK use spirometry regularly in their asthma clinics. Our recent research shows that a 10% fall in FEV1 over a 3-month period is followed by a 28% increased risk of an asthma attack in the next 3 months. We still do not know why using spirometry to guide treatment may lead to reduced attacks.

This research proposal will build on our previous research findings to answer the question "In children with asthma does spirometry and symptom guided treatment, compared to symptom guided treatment alone, reduce the number of asthma attacks?" In this study we also will further explore the links between treatment guided by spirometry and the risk of attacks.

We will recruit 550 children aged 6-15 years with asthma who have had an asthma attack in the last year. We already have a network of recruiting centres and have identified asthma clinics in hospitals and general practices who will recruit participants. Children will take part for 12 months. All children will meet the research team at the hospital or at a family doctor's premises every 3 months (this interval is commonly used in hospital asthma clinics). At the first meeting, permission to take part in the study will be obtained. Everyone that takes part will be put into one of two groups and has an equal chance of getting treatment in group 1 (treatment guided by spirometry plus asthma control (symptoms)) or group 2 (treatment guided by asthma control (symptoms) alone). All children will have spirometry measured at every visit. Asthma control (symptoms) and other asthma details will be gathered from questionnaires. A computer programme will guide treatment decisions based on symptom score, current treatment and also, in group 1, spirometry measurements. At 3- month intervals over a year, children will meet the research team, complete the symptom questionnaire, and spirometry, and have their treatment changed according to spirometry and asthma control (symptoms), or asthma control (symptoms) alone. We will measure asthma attacks and other outcomes over 12 months.

In partnership with Asthma UK we have discussed study design with parents and young people. They said a 30% reduced risk for asthma attacks was meaningful for them. Parents and young people have contributed to this plain English summary.

We will write a report which gives all our results. Our report will be published in a medical journal, given to the NHS, to participants and asthma guideline groups around the world.

Glossary of abbreviations

AE	Adverse Event
AUC	Area under the curve
BTS/SIGN	British Thoracic Society/Scottish Intercollegiate Guidelines Network
CACT	Children's Asthma Control Test
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
EME	Efficacy and Mechanism Evaluation
FEF_{25-75}	Forced Expiratory Flow at 25-75% of Forced Vital Capacity
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Exhaled Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GP	General Practitioner
HRQoL	Health Related Quality of Life
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ICS	Inhaled corticosteroids
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IVR	Interactive Voice Response (randomisation)
LABA	Long Acting Beta Agonist
LTRA	Leukotriene Receptor Antagonist
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute Health Research
NRES	National Research Ethics Service
OCS	Oral corticosteroids
PAQLQ	Paediatric Asthma Quality of Life Questionnaire
PI	Principal Investigator

PIC	Participant Identification Centre
PIL	Patient Information Leaflet
PMG	Project Management Group
PPIE	Patient and Public Involvement/Engagement
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SABA	Short Acting Beta Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen

Trial personnel

Chief Investigator

1 Professor Steve Turner

Grant Holders

1	Dr Ian Sinha	5	Dr Seonaidh Cotton
2	Dr Erika Kennington	6	Associated Professor Erol Gaillard
3	Dr Lorna Aucott	7	Mrs Beth Thompson
4	Professor Graeme MacLennan	8	Mrs Shakeela Riaz

Trial Office Team

1	Chief Investigator	5	Senior Trial Manager
2	CHaRT Director	6	Senior IT Manager
3	Trial Manager	7	Trial statistician
4	Data Co-ordinator		

Project Management Group (PMG)

This Group is comprised of the grant holders along with representatives from the Trial Office team.

Trial Steering Committee (TSC) Members

The membership of this Committee comprises independent members along with the Chief Investigator (CI; Steve Turner) or a nominated delegate. The other SPIROMAC grant-holders and key members of the Trial Office team (e.g. the trial manager) may attend TSC meetings. The terms of reference of the Trial Steering Committee, the template for reporting and the names and contact details of members of the TSC will be filed in the Trial Master File.

Data Monitoring Committee (DMC) Members

This Committee is comprised of independent members, and the trial statistician contributes as appropriate. The CI and/or a delegate may contribute to the open session of the meetings as appropriate. The terms of reference of the Data Monitoring Committee, the template for reporting and the names and contact details of members of the DMC will be filed in the Trial Master File.

Role of the Trial Sponsor and Funder

The Sponsor (co-sponsor) has responsibility for the initiation and management of the trial as defined by the UK Policy Framework for Health and Social Care Research v3.3 07/11/17. This is further defined within a co-sponsorship agreement outlining the roles and responsibilities

of the parties involved in the research. Specific responsibilities delegated to another party are formally agreed and documented by the Sponsor.

The funder has oversight of the study through regular reports from the trial office. The funder appoints the independent members of the Data Monitoring and Trial Steering Committees and receives minutes from these. The funder is made aware of all outputs from the study but does not have a role in the decision to publish results from the study. In any publications, the funder is acknowledged, and appropriate disclaimer used to indicate that the views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

1. Introduction

1.1 Background

What is the problem being addressed?

The problem being addressed is asthma attacks (also called asthma exacerbations) in children. A key goal in asthma management is to minimise the risk for asthma attacks[1]. Each year, 20% of the 1.1 million children with asthma in the UK has an asthma attack[2]. A child is admitted to hospital in the UK with an asthma attack every 20 minutes[2]. There are approximately 200,000 children treated annually for attacks with oral corticosteroids (OCS)[3], this is equivalent to an attack every 2.5 minutes. The high burden of asthma admissions in the UK relative to other European Union countries is a concern[4]. Deaths due to childhood asthma attacks in the UK are two-to-four times higher than other European countries per head of population[5]. The National Review of UK Asthma Deaths concluded that "46% of asthma deaths could have been avoided with better routine care"[6]. Our PPI co-applicants remark that fear of asthma attacks and the attacks themselves cause lots of anxiety for families.

In addition to morbidity and mortality, asthma has a negative impact on educational and economic outcomes. Asthma attacks cause 2.8 million lost school days per year[7] and every asthma attack means that one parent misses 4 days of work[8].

Many attacks can be prevented by regular routine care and appropriate asthma preventer treatment. There is a need for a validated objective test to guide preventer treatment. Current decision-making for asthma preventer treatment is subjective since it is guided by a clinician's interpretation of patient/carer-reported recent asthma control (symptoms). Spirometry is a commonly used simple breathing test which objectively measures lung function (i.e. how well the lungs are working). When measured by spirometry, lung function can be expressed as volumes and flows. The primary measurement is a flow called Forced Expiratory Volume in one second (FEV_1, the volume that can be forced out in one second after taking a deep breath). A spirometric measurement of volume is called Forced Vital Capacity (FVC, the total volume of air that can be forced out after taking a deep breath). Spirometry is recommended in some[1,9-11] (but not all[12]) guidelines as part of monitoring children with asthma. Guidelines do not say how treatment should change in the context of changing spirometry results[1,9-11].

Spirometry is a reproducible test of lung function[13] and can be obtained in >94% of school-aged children[14].

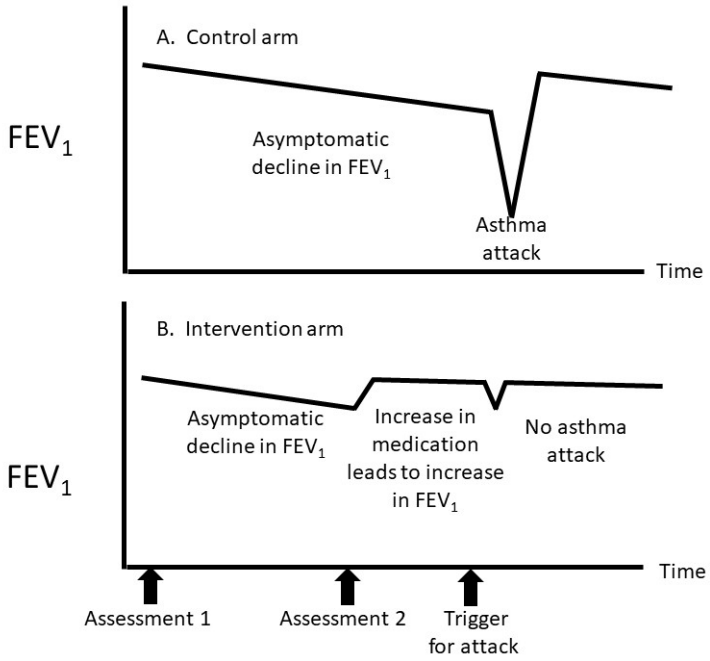
Clinicians are uncertain of the role of spirometry in guiding asthma treatment, and this means that spirometry is used inconsistently across UK asthma clinics. We have recently described this equipoise and shown that that in asthma clinics across the UK, spirometry is either measured as a matter of routine in 24% of clinics surveyed, or on a case-by-case basis or not at all in the remaining 76%[15]. SPIROMAC will be the first study to rigorously evaluate how spirometry (and specifically FEV_1) can be used to guide asthma treatment and potentially reduce the risk for asthma attacks. Our innovation is to use spirometry plus asthma control (symptoms) to guide asthma preventer treatment with the aim of reducing

asthma attacks. We will use a randomised controlled trial to minimise confounding for factors associated with asthma attacks. The mechanistic component of our study will explore the link between treatment decisions being informed by spirometry and attacks.

There is no randomised controlled trial evidence to explain how treatment decisions informed by spirometry lead to reduced asthma attacks. The causal pathway to an asthma attack is complex and includes the following: a trigger for the attack; reduced spirometry measurement at the time of exposure to the trigger for an attack; increased eosinophilic (or allergic) airway inflammation at the time of exposure to the trigger; the level of asthma preventer treatment; adherence to asthma preventer treatment; and factors associated with health seeking behaviour (including asthma education/knowledge, deprivation, age and ethnicity).

The mechanism where spirometry-guided asthma management may lead to reduced asthma attacks is illustrated in Figure 1.

Figure 1. A stylised figure illustrating one possible mechanism, which will be explored in SPIROMAC, for how spirometry guided treatment may reduce the number of asthma attacks. The same child would have an attack in the control arm (panel A) but the intervention would prevent the attack from occurring (panel B).



- In the upper panel (A), an individual in the control arm with good asthma control (no symptoms) has a decline in spirometry (as evidenced by FEV_1) in the weeks and months before having an asthma attack. We know that a fall in FEV_1 over three months (equivalent to the interval between assessments 1 and 2) is associated with increased risk for a subsequent attack[16]. During the attack lung spirometry falls[12] and then recovers due to oral corticosteroid treatment.
- In the lower panel (B), a symptom-free decline in FEV_1 is detected at assessment 2, asthma preventer treatment is changed leading to increased FEV_1. The subsequent

exposure to a trigger leads to a small fall in FEV_1 but there is no asthma attack because spirometry values are higher at the time of exposure to the trigger.

Why is the research important in terms of improving the health of the public and/or to patients and the NHS?

Asthma is the most common childhood chronic disease in the UK[2]. As explained in the previous section, asthma attacks cause morbidity and sometimes mortality, impact on the quality of life of the child and their family and are a huge cost to the NHS. NHS resources used during an asthma attack may include contacting NHS24 for advice, unscheduled presentation (to general practice, the out-of-hours service or emergency department), calling an ambulance and being admitted to a paediatric ward, high dependency or intensive care unit. At least one third of the £1.1 billion spent by the NHS on asthma care per year[2] is incurred in the provision of unscheduled asthma care, and knowing that 20% of asthmatics are children[2] the annual cost attributable to unscheduled asthma care for children is at least £73 million. Attacks are more common in children than adults meaning that the actual annual NHS spend on managing childhood attacks is probably in excess of £2 million every week.

An evidence base from SPIROMAC would inform NHS England's Long Term Plan to increase access to spirometry testing via the new Primary Care Training Hubs from 2020/21[17].

SPIROMAC could contribute to an improvement in the health of the UK public by providing a method to reduce asthma attacks in children and describing how the methodology works. Reducing asthma attacks will reduce morbidity and mortality and reduce the cost to the NHS of unscheduled care. Our PPI co-applicants note that reduced asthma attack would improve educational and physical confidence and reduce strain on families.

1.2 Rationale for the trial

Research is required now as there is inconsistency within UK and international asthma guidelines on the role of spirometry in asthma management. Importantly, there is weak or no evidence underpinning those guidelines which recommend spirometry should be used as part of asthma management. One of five current asthma guidelines[1] cite a single observational study[18] to support the role of spirometry in monitoring asthma. Three guidelines, including one for the UK,[9-11] cite no supporting evidence but also recommend that spirometry should be done. A second UK guideline[12] does not recommend regular spirometry in children. Two guidelines suggest that treatment could be changed when FEV_1 is <80 percent of predicted values (%)[9,10]. No guidelines give evidence-based or clinically meaningful guidance for clinicians to act on spirometry results. For example, what change in spirometry should prompt a change in treatment in an asymptomatic child? And which treatment should be changed? And what the change should be to? Proof-of-concept that a structured approach to asthma management, including routine use of spirometry, benefits children comes from Norway where there was a 61% fall in children presenting to the emergency room with asthma after implementation of standardised management[19].

Given the lack of evidence and conflicting recommendations by UK and international guideline groups, it is not surprising that there is uncertainty within the clinical community whether spirometry is beneficial in guiding asthma preventer treatment. Amid this

uncertainty, asthma attacks in the UK continue to be common[2], there is clinical equipoise[15] and we have recently published proof-of-concept data upon which to design our research[16].

SPIROMAC will be the first study to rigorously evaluate how spirometry can be used to guide asthma treatment and reduce the risk for asthma attacks in children. FEV_1 is the preferred spirometric index in asthma clinical trials[20] and this will be the principal spirometry measurement used in SPIROMAC. We will also use FVC as a second spirometry measurement. A systematic review of risk factors for asthma attacks in children did not identify any index of reduced lung function (including spirometry) as a risk factor[21]. However, our review of the literature identified five original articles[16,18,22-24] which report associations between a "low" value of FEV_1 on a single occasion and increased risk for future asthma attacks; the period of follow up after the FEV_1 measurement were three months[16], twelve months[18,22], three years[23] and four years[24]. An additional paper[25] found that FEV_1 results are within the normal range (i.e. between 80 and 120%) in most children with asthma, and this means that using one-size-fits-all cut-off values to trigger change in treatment is unhelpful in identifying individuals at risk for attack, e.g. FEV_1<80% is recommended in some guidelines[9,10]. A further limitation of using one-size fits all cut offs is that some asymptomatic individuals have an FEV_1 persistently <80% (i.e. always "abnormal")[9,10].

An individualised approach to interpreting spirometry values may be more meaningful to risk of future asthma attacks[1], e.g. a reduction from 100% to 90% may be clinically meaningful even though these measurements fall within the "normal range". Our observational study[16], published in 2019, describes how a 10% fall in FEV_1 over a three-month interval where children had good asthma control and FEV_1 was within the "normal" range was associated with a 28% increased risk for an asthma attack over the next three months. Our PPI work has identified that parents believe that a 28% increased risk is meaningful. "A 30% prevention to a child admitted to hospital 15 times over five years would reduce it to 11 admissions. Surely even a reduction of one admission would be worth it?"

A further reason for SPIROMAC being timely is the recognition that asthma is a heterogeneous condition[26], and a one-size-fits-all approach to asthma preventer treatment is not appropriate. Asthma preventer treatment includes inhaled corticosteroids (ICS), long acting beta agonists (LABA) and leukotriene receptor antagonists (LTRA). The SPIROMAC treatment algorithm will not deliver one-size-fits-all recommendations for participants in the intervention arm. For example, a child with poor asthma control on low dose ICS will have LABA commenced if their FEV_1 has fallen by >10%. In comparison, a child with poor asthma control on low dose ICS whose FEV_1 has not fallen by 10% will have their ICS dose increased (or LTRA treatment started if the participant is already prescribed intermediate dose of ICS).

We have established that there is an element of equipoise across the UK in the application of spirometry to asthma monitoring[15]. We contacted 34 principal investigators recruiting to our RAACENO study (an ongoing asthma clinical trial[27]) and asked if they would be able to recruit to SPIROMAC after explaining the study design and inclusion criteria. All centres replied. Whilst many centres do not use spirometry routinely, there were 8 centres who felt unable to recruit since spirometry was standard practice in their unit.

Our methodology will use a computer-based treatment algorithm to standardise asthma preventer treatment across all sites for participants in the standard care and intervention arms of the trial. We will objectively measure adherence to ICS preventer treatment with an electronic logging device. We will ensure that inhaler technique is satisfactory on each assessment. We will blind all participants to the spirometry results in case this knowledge alters risk for attack, e.g. by affecting adherence to asthma preventer treatment. Randomisation will minimise confounding by health seeking behaviour and associated factors.

The only similar trial currently under way of which we are aware is RAACENO[27]. RAACENO is a trial lead by our group which will determine whether in children with asthma, asthma preventer treatment guided by symptoms and Fractional Exhaled Nitric Oxide (FeNO) compared to symptoms only is associated with reduced asthma attacks.

1.3 Assessment and management of risk

The CI will ensure, through the TSC, that adequate systems are in place for monitoring the quality of the study (compliance with GCP) and appropriate expedited and routine reports of adverse events, to a level appropriate to the risk assessment of the study.

Families will be informed of the possible benefits and disadvantages of taking part by means of information leaflets, discussion with local research nurses and the asthma team. The policies of recommending treatment based on asthma control (symptoms) only and based on spirometry plus asthma control (symptoms) are both used routine within the NHS. We do not anticipate that participants will run additional risks by participating in SPIROMAC. Parent/carer(s) of children will sign a consent form approved by the Ethics Committee. Children or families who are not willing to be randomised will not be recruited.

COVID-19 risks

Although use of spirometry was suspended at the outset of the COVID-19 pandemic, it has been re-introduced into asthma care and asthma clinics across the UK. Similarly, routine asthma clinics were moved to a remote model at the outset of the COVID-19 pandemic, however many routine clinics have reverted to face-to-face appointments.

Children with asthma are not at any increased risk of either contracting COVID or of serious illness from COVID than the general population of children. Compared to children without asthma they are less likely to require treatment in ICU as a result of COVID. They are not included in the high-risk classification.

During face-to-face contact, appropriate COVID-19 precautions will be taken (for example social distancing, hand hygiene) to mitigate risks. Any prevailing guidance from a national, regional or local trust level will also be adhered to.

If face-to-face contact is not possible at any point during the study, recruitment to the study would be paused. Follow-up of existing participants might be delayed or done remotely (by telephone or video call) which would mean that spirometry measurements might not be done – for further information see section 7.3.

The Funder, Trial Steering Committee and Data Monitoring Committee will review the accumulating data regularly to assess the impact of any COVID-19 restrictions on the SPIROMAC study.

2. Trial aim and objectives

The aim of the study is to compare treatment guided by spirometry plus symptoms against treatment guided by symptoms alone (standard care), in children with asthma who are at risk of an asthma attack. There are efficacy and mechanism aims:

(i) Efficacy. To determine the efficacy of treatment guided by spirometry plus symptoms compared to treatment guided by symptoms alone in children with respect to: asthma attacks up to 12 months post randomisation; and asthma control (symptoms); health-related quality of life; adverse events and dose of inhaled corticosteroids.
(ii) Mechanism. To determine how treatment guided by spirometry plus symptoms (compared to treatment guided by symptoms only) leads to improved air flow (FEV_1), lung volume (FVC) and reduced eosinophilic airway inflammation (Fractional Exhaled Nitric Oxide, FeNO) and is associated with reduced attacks.

2.1 Research questions

(i) In children with asthma does treatment guided by spirometry plus asthma control (symptoms) compared to treatment guided only by symptoms reduce the number of asthma attacks?
(ii) Our mechanistic question is: is the effect of spirometry-guided treatment in reducing asthma attacks mediated through change in lung function and/or eosinophilic airway inflammation?

2.2 Hypotheses

We hypothesise that asthma treatment guided by spirometry will improve flow and volumes, and that this will lead to reduced asthma attacks. SPIROMAC will therefore determine whether the spirometry-guided treatment reduces attacks by achieving one or more of the following:

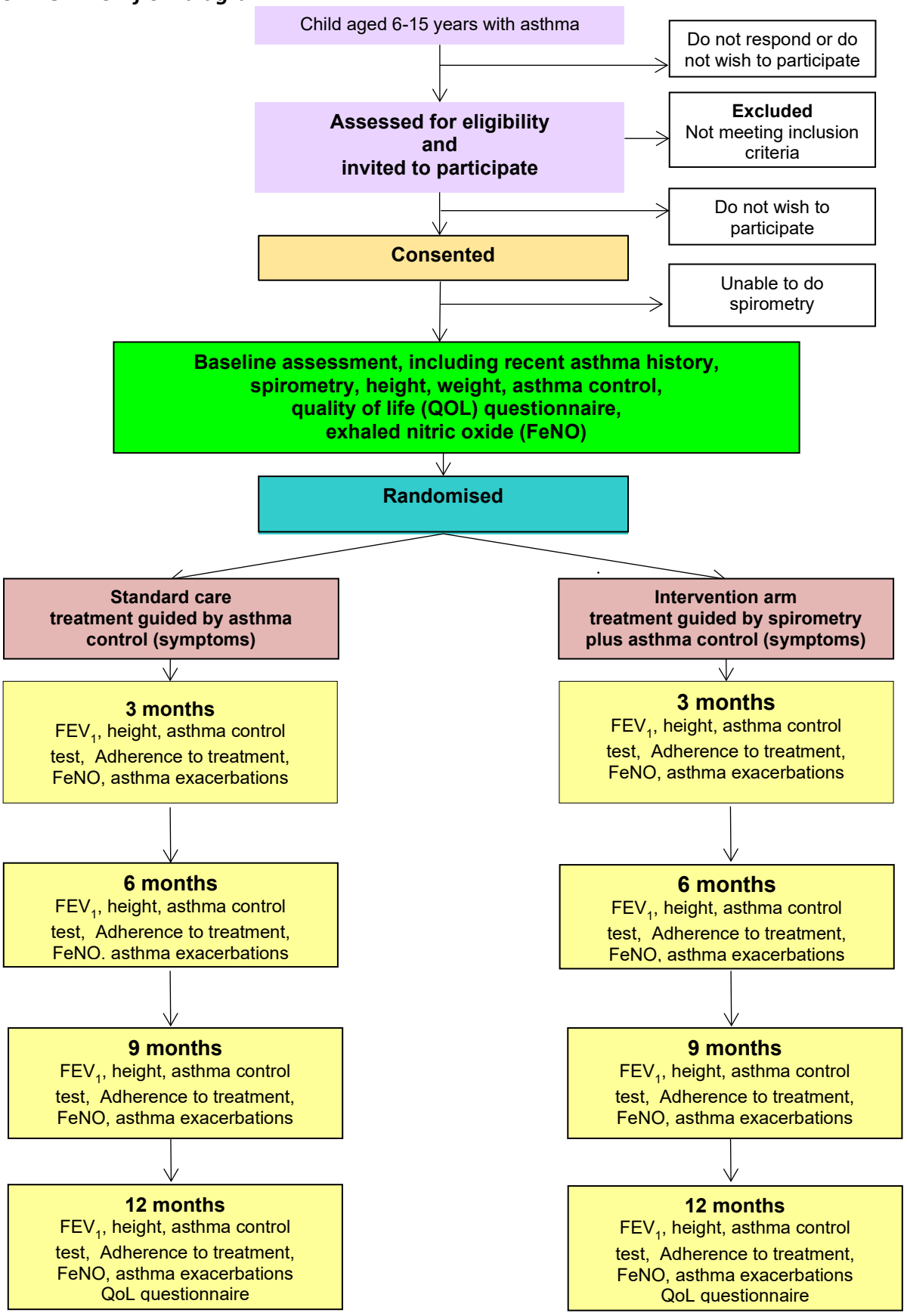
- Increased spirometry measurement as evidenced by improved airway flow (FEV_1)
- Increased spirometry measurement as evidenced by improved lung volume (FVC)
- Reduced eosinophilic airway inflammation, as evidenced by FeNO[28]. The mechanistic aim has eosinophilic airway inflammation as an intermediary on the mechanistic pathway we will explore between treatment guided by spirometry plus symptoms (the effector) and reduced asthma attacks (the outcome). Eosinophilic inflammation may be relevant to attacks independently of lung function (as evidenced by FEV_1 and FVC). FeNO is not part of the SPIROMAC treatment algorithm and is being measured to give this mechanistic insight.

3. Trial Design

A randomised controlled trial comparing asthma treatment guided by spirometry plus symptoms compared to treatment guided by symptoms alone. We will measure spirometry in all participants, and FEV_1 will be used within an algorithm to guide treatment in the intervention arm. All participants, carers and usual clinical teams will be blinded to spirometry results. A nine-month internal pilot phase will assess recruitment, equipoise,

feasibility and acceptability of the algorithm and quality of data collected and inform progression to full trial. A flow-diagram is provided below.

SPIROMAC – flow diagram



4. Intervention being evaluated

The arms are as follows:

- Intervention: treatment guided by spirometry plus asthma control (symptoms)
- Standard care: treatment guided by asthma control (symptoms)

In both arms, the same data will be recorded on the study website. The treatment algorithm that will guide treatment will be embedded in the study website, and will take into consideration the following data at baseline and follow-up.

	Standard care		**Intervention**	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
Asthma Control (ACT/CACT; three categories)	✓	✓	✓	✓
Adherence	✓	✓	✓	✓
Asthma attack in last three months	✓	✓	✓	✓
Step up in treatment since last study visit				
SABA use	✓	✓	✓	✓
Current treatment	✓	✓	✓	✓
FEV_1			✓	✓

At each visit, the study local study team can agree with the treatment recommendation, or over-ride the recommendation and make their own recommendation for the asthma treatment for the next three months. If they wish to make their own recommendation for asthma treatment, they will be asked to document the reason for this and the treatment they are recommending. The study website will generate a summary of any treatment change (or that there is no change) for the family, for the participant's GP, and, for those recruited in hospital, for the hospital asthma team.

The treatment algorithm is described in appendix 1.

In both arms of the study, if a child is on maximum levels of treatment for their age, it will not be possible to step-up treatment within the treatment algorithm – in such cases, the treatment algorithm will recommend that the asthma team (or GP in primary care) makes a decision about treatment for the next three months. In addition, in children where adherence to treatment is poor (<70% recommended doses), only one step up in recommended treatment will be made, and after that efforts will focus on improving adherence rather than further increasing treatment.

In the intervention arm, if there are minimal changes to the FEV_1 (less than 7%) but the ACT/CACT scores are less than 13 (poor control) on successive visits, there will be a recommendation to increase treatment at the first visit, but at the second visit, the recommendation will be for the asthma team (or GP in primary care) to review the participant and make a decision about treatment for the next three months. Similarly, if the FEV_1 drops by more than 7% on two separate visits, only the first drop will trigger a recommendation to increase treatment.

5. Trial recruitment

5.1 Trial population

Children aged 6-15 years with asthma confirmed by a clinician, who have had an asthma attack in the previous year and are able to provide a spirometry measurement. The trial will be set in both secondary and primary care.

5.2 Inclusion and exclusion criteria

Inclusion criteria:

- Aged 6-15 years
- Asthma diagnosis confirmed by a doctor or a respiratory/asthma specialist nurse (or Read code for asthma if recruited in primary care)
- patient/parent reported-asthma attack treated with at least one course of oral corticosteroids in the 12 months prior to recruitment
- Be able to perform spirometry
- Be able to understand written/spoken English.

Exclusion criteria:

- Not being able to perform spirometry satisfactorily
- Presence of another chronic respiratory condition (e.g. cystic fibrosis)
- Current treatment with maintenance oral steroids* and biologicals (we cannot provide standardised step up/down treatment options).

* If the child has previously used maintenance oral steroids, or have recently had an asthma attack they would be eligible after a period of at least 2 weeks since ceasing oral steroid treatment.

5.3 Identifying and approaching participants

In secondary care, the local clinical team responsible for patient care will identify eligible children from paper and electronic records. The initial approach will be in person (at a clinic appointment) by a member of the usual care team (which may include embedded research nurses), or by letter/email from the managing clinician or asthma specialist nurse. For those approached in clinic, the parent and child patient information leaflets (PIL) will be handed to the family by a member of the usual clinical team. At this time, the parent will be asked whether they would be happy for a member of the study team to speak to them in the clinic or to contact them by telephone to answer any questions they may have about the study. For those approached by post or email, the parent and child patient information leaflets (PIL) and letters of invitation will be sent to the family by the managing clinician or asthma specialist nurse. Those interested in taking part in the research can contact the research team either by telephone or by returning the reply slip in a pre-paid envelope. A member of the usual care team (which may include embedded research nurses) may contact the parent by telephone around two weeks after the initial approach to answer any questions they have about the study.

Practices can act as Participant Identification Centres for secondary care (or other primary care) sites. NRS Primary Care Network staff, CRN staff or staff employed in the primary care

practice will identify eligible children from general practice records. The initial approach will be by letter, from a GP in the practice. This will be sent with the short PIL. Those interested in taking part in the research will be asked to contact the research team based at the recruitment site either by telephone or by returning the reply slip in a pre-paid envelope. Interested families will then be sent the parent and child patient information leaflets and arrangements made for those who wish to take part to be seen at the recruitment site for a recruitment appointment.

In primary care, primary care or CRN staff will identify eligible children from general practice records. The initial approach will be by letter, from a GP in the practice. The parent and child PILs and letters of invitation will be sent to the family or handed to the family by the managing clinician. As above, those interested in taking part can telephone the research team or return the reply slip in a pre-paid envelope.

Alternatively, in both secondary and primary care, the short PIL can be sent/given to the family with the invitation letter. Families who express interest in taking part will be sent the longer parent and child patient information leaflets before attending a recruitment appointment.

5.4 Informed consent

For families who are interested in participating in the study, a recruitment appointment will be arranged either in secondary or primary care. At this recruitment appointment, consent will be sought according to Good Clinical Practice (GCP). Written consent will be obtained from parent(s)/carer(s) and (where appropriate) from the participant. If the child does not provide written consent, they will be asked to give verbal assent.

Children who turn 16 during follow-up may wish to re-consent to their continued participation at the next follow-up visit by signing a new consent form. They will be given a participant information leaflet. If they do not wish to do this, the study team will confirm verbally that they are happy to continue taking part in the study and note this in the medical notes and the eCRF.

5.5 Randomisation and allocation

Eligible and consenting participants are randomised to one of the two groups (treatment decisions based on spirometry plus symptoms [*intervention* arm] or treatment decisions based on symptoms alone [*standard* care]) using the proven 24-hour web-based randomisation application hosted by CHaRT.

Random allocation will use a minimisation algorithm (stratification by centre [*for primary care sites this will be by primary care area*], age (<12 years, ≥12 years), sex and asthma severity as evidenced by BTS/SIGN treatment step (BTS step 2, BTS step 3, BTS step 4, BTS step 5; other [*we will use the "other" category for children on an non-standard treatment regimen that cannot be immediately classified into a BTS step*]) including a random element (20%). The primary care centres will be collectively considered as one centre for randomisation.

5.6 Blinding

The study will be blinded. When the participant is randomised, the allocation will not be divulged to the staff at the site or to the participants themselves. Spirometry data is collected in both arms. The treatment algorithm will be embedded into the study website. Regardless of which arm the participant is randomised to, the site staff will enter data on symptoms and spirometry (and, at the follow-up visits, adherence to preventer treatment) into the study website. In participants randomised to asthma treatment guided by spirometry plus symptoms, the web-based treatment algorithm will consider the spirometry results. In participants randomised to asthma treatment guided by symptoms alone, the web-based treatment algorithm will not consider the spirometry results.

As longitudinal data on spirometry and symptoms for an individual child accumulates, it may be possible for staff to make an informed "guess" as to which arm a child is in using the detailed decision trees that sit behind the treatment algorithm. If they do this, they will be encouraged not to share this information with the family.

Staff in the study office will have access to the randomised allocation in order to check (where necessary) that the treatment algorithm is performing correctly.

5.7 Code break/Emergency unblinding procedures

There is no requirement for emergency unblinding procedures. This is because knowledge of whether a participant is in the control or intervention group would not impact on any management decisions being taken if an adverse event occurs.

5.8 Administration arrangements post recruitment (if applicable)

The GP will be informed in writing when a participant joins the study; the letter will include any treatment decisions made at the recruitment appointment. They will also be informed of any treatment decisions following the 3, 6 and 9 month follow-up visits. After the 12 month follow-up visit, the GP will be informed of any treatment decision, and also that the participant has completed follow-up within the study. These letters will be signed by the local research team and generated by the study website from information entered during baseline and follow-up visits. Letters to GPs will be generated by site staff immediately after the study visit (see section 5.1 for more detail). When issuing the GP letter following a telephone follow-up it will be clearly documented that the visit was carried out by telephone. If there is a change in treatment the family (and GP) will be informed as to how the change should be enacted (see section 5.1.2 for further details).

The local Research Nurse/Recruitment Officer and/or PI will:

i) file a copy of the consent form in the hospital/primary care notes along with information about the study.
ii) file a copy of the GP letter into the hospital/primary care notes.
iii) enter study data regarding the participant into the bespoke study website.
iv) maintain study documentation at site. A copy of the signed consent form will be returned to the Study Office in Aberdeen.
v) provide any relevant follow-up clinical data.

If a participant withdraws from the study during the follow-up period (see also section 7.5), the local research team will write to the GP informing them of this.

Participants will be contacted by telephone, post or email as appropriate. In case of non-attendance at follow-up clinic appointments or non-return of questionnaires, attempts will be made by site staff or staff at the Study Office to trace the participant directly using these means or indirectly by contacting the GP.

5.10 Non-recruited participants

The following anonymized information will be collected for potentially eligible participants:

- Age
- Reason not eligible
- Reason for not participating, if willing to give a reason.

5.11 Co-enrolment

Participants will be permitted to take part in non-interventional studies (e.g. questionnaire studies). Those enrolled in the active intervention phase of another interventional trial will be excluded but they would be eligible for inclusion if they are now in the long term follow up phase of such trials.

6. Outcome measures

6.1 Primary outcome measure

The primary outcome for our study is number of asthma attacks per participant which require treatment with 1-7 days oral corticosteroids (OCS) and/or intravenous corticosteroids up to 12 months post randomisation reported by participant or parent/carer. This definition of an asthma attack is a recommended outcome for clinical trials in asthma[29]; however if standard treatment practices for asthma attacks change during the lifetime of the project, the definition of the primary outcome will be reviewed to ensure all relevant asthma attacks are captured. There is a UK national guideline which standardises OCS prescribing for an asthma attack in children[12]. For participants lost to follow-up, the primary outcome will be determined from primary and secondary care records by research nurses within each centre.

6.2 Secondary outcome measures

The secondary outcomes include:

- any asthma attack (yes/no)
- time to first asthma attack
- Asthma control (participant reported asthma symptoms; using Asthma Control Test (ACT) or Children's Asthma Control Test (CACT) as appropriate)
- quality of life measured using the Paediatric Asthma Quality of Life Questionnaire (PAQLQ)
- adverse events
- dose of inhaled corticosteroids (ICS)

Additionally, spirometry measurements and FeNO during the 12 month follow-up will be included as outcomes in the mechanistic analysis.

7. Data collection and processing

7.1 Measuring outcomes

Table 1 below summarises which outcomes/measurements will be collected at each time point.

Table 1. Timing of outcome measures

	Baseline assessment	Three-month assessment	Six-month assessment	Nine-month assessment	Twelve-month assessment
Baseline characteristics, including recent asthma history	✓				
Spirometry	✓	✓	✓	✓	✓
Height	✓	✓	✓	✓	✓
Weight	✓				
Asthma Control Test	✓	✓	✓	✓	✓
Paediatric Asthma Quality of Life Questionnaire	✓				✓
Primary outcome (asthma attack)		✓	✓	✓	✓
Adherence to ICS treatment (from Smartinhaler device)		✓	✓	✓	✓
Exhaled nitric oxide (FeNO)	✓	✓	✓	✓	✓

Asthma attacks. The primary outcome is captured from parental report at the three-monthly follow up assessments. Where data are not available at twelve months, the general practice (GP) at which the participant is registered will be contacted to capture primary outcome data. Our previous study (RAACENO, NIHR 15/84; ISRCTN 67875351) has any parent-reported asthma attacks (yes/no) as its primary outcome, and primary outcome data was secured in over 99% of participants

Asthma control. The ACT[30](or CACT for those aged <12 years) will be used to objectively determine asthma control. We will use three "control states" fully controlled, partly controlled or uncontrolled. An ACT/CACT of <20 indicates that the individual is inadequately controlled (but not necessarily uncontrolled). An ACT/CACT of <13 indicates the lowest level of control. In RAACENO the lower quartile value for ACT at baseline was 14.

Asthma quality of life. The PAQLQ will be used (with permission) at baseline and at the final assessment[31].

Spirometry. This will be measured by staff with Association of Respiratory Technology and Physiology qualification and in accordance with the international guideline[32], or by staff who do not have ARTP qualification but who have either received in-house training, or by staff who already undertake this activity as part of their routine NHS activity (or have previously done so). We know from RAACENO that this can be done in primary and secondary care. Spirometry will be standardised according to the Global Lung Initiative[33]. A clinically significant reduction in spirometry will be defined as FEV_1/FVC below the lower limit of normal at the baseline assessment and at the following assessments as a fall in FEV_1 of >7.0% [16] from the previous assessment.

Exhaled nitric oxide. Measurements will be made in accordance with the standard methodology[34] using the NIOX Vero ® device (Circassia, Oxford, UK). These results will not contribute to the treatment algorithm but are key to the mechanistic aspect of the study.

Electronic logging device. Smartinhaler devices will be used to electronically log adherence to ICS treatment and these data will be downloaded at each follow- up visit. We know that >90% of ICS inhalers in common use have a compatible Smartinhaler. Parent/carer-reported adherence will also be determined at all visits. The definition of adequate adherence is either >70% adherence as measured by the Smartinhaler electronic logging device or by participant/parent report of being adherent "most of the time" or "all of the time" (these definitions have been used in RAACENO). This definition allows for situations where Smartinhaler data are not available, e.g. at baseline assessment, failure of the device or non-availability of the device (including where compatible Smartinhaler devices are not available for the preventer treatment, e.g. Qvar autohaler, Asmabec clickhaler, Budelin Novolizer, Asmanex Twisthaler, Relvar Ellipta), and also the real-world scenario where there is a discrepancy between the Smartinhaler data and participant/parent report.

7.2 Baseline

At baseline, the web-based case report form (CRF) will record the participant's details (age, sex, respiratory information (including current treatment, past history), co-morbidities, family history, etc.). Information about inhaler technique will also be recorded on the CRF.

The baseline CRF will also capture measurements including spirometry, height and weight, and FeNO.

In addition, at the recruitment appointment, children and their parent/carer attending the appointment will be asked to complete an asthma questionnaire. For children aged 11 and under, the questionnaire will comprise the CACT and the PAQLQ. For children aged 12 and over, the questionnaire will comprise the ACT and the PAQLQ.

For all children, data from the CACT/ACT and the spirometry results will be entered into the study website and, based on the treatment algorithm, the study website will recommend a change to existing treatment or no change to existing treatment (see section 4 for further detail). The study local study team can agree with the treatment recommendation, or over-ride the recommendation and make their own recommendation for the asthma treatment for the next three months. If they wish to make their own recommendation for asthma

treatment, they will be asked to document the reason for this and the treatment they are recommending. The study website will generate a summary of any treatment change (or that there is no change) for the family, for the participant's GP, and, for those recruited in hospital, for the hospital asthma team.

At the recruitment appointment, a SmartInhaler (if available) will be given to participants.

At the end of the recruitment appointment, a diary card will be given to participants. This can be used by participants and their parent(s)/carer(s) to document any asthma attacks and the treatment for these. If it is brought back to follow-up appointments, it will act as an aide memoir to recollect outcome data.

7.3 Follow-up

At the 3, 6, 9 and 12 month assessments, the web-based CRF will record spirometry, height, and FeNO. Adherence (Smartinhaler) data will be downloaded and recorded in the web-based CRF, along with a family-reported assessment of adherence.

Inhaler technique will be checked at each assessment.

Children and their parent/carer attending the appointment will be asked to complete an asthma questionnaire (for children aged 11 and under, the CACT; for children aged 12 and over, the ACT). They will also be asked about any asthma attacks.

At each appointment, for all children, data from the CACT/ACT, the spirometry results and adherence will be entered into the study website and, based on the treatment algorithm, the study website will recommend a change to existing treatment or no change to existing treatment (see section 4). The study local study team can agree with the treatment recommendation, or over-ride the recommendation and make their own recommendation for the asthma treatment for the next three months. If they wish to make their own recommendation for asthma treatment, they will be asked to document the reason for this and the treatment they are recommending. The study website will generate a summary of any treatment change (or that there is no change) for the family, for the participant's GP, and, for those recruited in hospital, for the hospital asthma team.

To facilitate measurement of lung function, FeNO and download of adherence data, face-to-face visits are the default method of follow-up within SPIROMAC. However, if a face-to-face follow-up assessment is not possible, follow up by telephone or video call is acceptable. Where the assessment is carried out by telephone, it will not be possible to do spirometry, measure FeNO or download adherence data from the SmartInhaler. In such cases, family reported adherence should be captured. The treatment algorithm (for both arms) can be run without spirometry measurements or Smartinhaler data. In the intervention arm, in the absence of spirometry, the symptom-only algorithm will apply.

The study website will generate a summary of any treatment change (or that there is no change) for the family, for the participant's GP, and for those recruited in hospital, for the hospital asthma team. The letter generated following the 12 month assessment will include

a recommendation for a hospital review in 3-6 months (or GP review for those recruited in primary care).

In addition, at the 12 month assessment, the participant (with the assistance of parent/ caregiver for younger children) will be asked to complete the PAQLQ.

Those who do not attend for follow-up at 3, 6 or 9 months will be contacted by telephone and another appointment made. There will be a six week window before and after each assessment date for that assessment to take place. As noted above, if a face-to-face visit is not possible, the appointment can be conducted by telephone or video call. In such cases, it will not be possible to for the child to do spirometry. Spirometry data is not required to run the treatment algorithm in the standard care arm, so the treatment algorithm will be executed as normal. Where spirometry data is not available for children in the intervention arm, the treatment algorithm will apply the standard care decision tree which does not require spirometry data. Those who do not attend for face-to-face follow-up or where telephone follow-up is not possible will be sent a brief questionnaire by post comprising the CACT/ACT and asking about any asthma attacks since their last visit. The treatment algorithm will not be executed for these participants and they will remain on current treatment unless this is changed outwith the study.

Those who do not attend for follow-up at 12 months will be contacted by telephone and another appointment made. There will be a six week window before and after the assessment date for that assessment to take place. As noted above, if a face-to-face visit is not possible, outcome data can be collected by telephone or video call. Those who do not attend face-to-face follow-up or where telephone follow-up is not possible will be sent a brief questionnaire by post comprising the PAQLQ, CACT/ACT and asking about any asthma attacks since their last visit.

7.4 Capture of data from medical records (if appropriate)

Where patients fail to attend for follow-up at 12 months and do not provide outcome data by telephone or on the brief questionnaire, the research nurse at site or the trial office will contact the GP practice at which the participant is registered to try and capture primary outcome data: number of asthma attacks treated with OCS since the last contact with the participant. The time to first OCS course will also be requested.

7.5 Change of Status/Withdrawal procedures

Participants remain in the trial unless they choose to withdraw consent or if they are unable to continue for a clinical reason. Participants are free to withdraw from the trial at any timepoint. Participants who have never had the intervention or have received the other (non-allocated) intervention remain in the trial and are followed-up for all trial outcomes unless they request otherwise. All changes in status with the exception of complete withdrawal of consent means the participant is still followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal is retained and used in the analysis.

If participants withdraw from the intervention or control (or trial treatment), they are asked to consider if they wish to remain in the trial and be followed up as per trial schedule.

Participants who wish to withdraw from active trial follow-up are asked if they wish to allow routine follow-up data from hospital or GP records to be used for trial purposes.

Participants who do not attend for follow-up assessment but for whom any outcome data are available are included in an intention to treat analysis.

Cross-over within the study (i.e. those in the intervention arm not completing lung function measurements, or the use of lung function measurements in someone in the control arm) will not result in withdrawal from the study. Participants will be included in an intention to treat analysis. Cross-over may be temporary (for example if the spirometry equipment or technician is not available to measure lung function at a specific appointment), or permanent (for example participants in the intervention arm may decide that they no longer wish to have their treatment informed by spirometry).

7.6 Data processing

Research nurses at each centre will enter locally collected data into the study website. As the treatment decisions are protocolised via the study website (see section 4), the data entry will be done in real-time to allow for any treatment step-up/down decisions to be communicated with participants and their families at the clinical appointment.

Staff in the Trial office will work closely with local Research Nurses to ensure the data are as complete and accurate as possible. Follow-up questionnaires to participants unable to attend for follow-up will be sent from and returned to the Trial Office in Aberdeen (or, if sites prefer, sent from and returned to the site team). Data from questionnaires returned to the trial office will be entered into the study website by trial office staff. Extensive range and consistency checks will further enhance the quality of the data.

7.7 Pharmacogenetic component

As part of a pharmacogenetic component of SPIROMAC, children can opt to provide a saliva sample – either at baseline, or any of the subsequent follow-up visits. These samples will be used to study pharmacogenetics in asthma which will inform the results of both the SPIROMAC study and pharmacogenetics more widely. The primary variant of interest is the Arg16Gly single nucleotide polymorphism of the gene coding for the beta 2 adrenoceptor; individuals who carry one or two of the Arg alleles are known to be at increased risk for asthma exacerbations if they receive treatment with long-acting beta agonist. Any results will contribute to an international collaboration on Pharmacogenetics in Children with Asthma (the PiCA collaborative).

Participants who opt into this optional mechanistic component of the study will have the saliva collection done at the end of the assessment. A sample of salvia will be collected into a receptacle. Samples will be labelled with the participant's study number and date of collection but not with their name, date of birth or any personal details. If commercial saliva testing kits are available at the site, manufacturer's protocol for collection if saliva will be followed. These can be returned to Aberdeen in the kit packaging at ambient temperature (without the need for dry ice). If commercial saliva testing kits are not available at site, the participant will rinse their mouth for 20 seconds with 10 mls tap water and spit the fluid into a universal container which will be labelled and stored at

minus 20 degrees or below. Samples will be sent to Aberdeen on dry ice in batches for secure storage at minus 80 degrees in the University of Aberdeen Child Health freezer. We will keep records of when samples are shipped from sites to Aberdeen and also of receipt. When funding is available, samples will be thawed (if appropriate) and DNA extracted prior to analysis of genetic variants associated with asthma and allergy outcomes. The primary variant of interest is the arg16gly single nucleotide polymorphism of the gene coding for the beta 2 adrenoceptor. Laboratory protocols will be in place to handle samples as being potentially COVID-19 positive. Consent for DNA testing of these samples will be sought at the outset of the study. After testing, any residual sample will be destroyed. If we are not successful in securing funding to test these samples, they will be destroyed two years after SPIROMAC has been completed.

8. Safety

8.1 Standard definitions

Term	Definition
Adverse Event (AE)	Any untoward medical event affecting a clinical trial participant.
Serious Adverse Event (SAE)	Where an AE • results in death; • is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe); • requires hospitalisation or prolongation of existing hospitalisation; • results in persistent or significant disability or incapacity; • is a congenital anomaly or birth defect, • is otherwise considered medically significant by the investigator

8.2 Trial specific considerations

Spirometry equipment and the NIOX VERO (used to measure FeNO) are CE certified and known to be safe for use in this age group. Within SPIROMAC, we will only record any Adverse Events (AEs) and Serious Adverse Events (SAEs) relating to use of spirometry equipment, the NIOX VERO or other study assessments.

An asthma attack (defined as an increase in asthma symptoms requiring treatment with oral corticosteroids) is the primary outcome and is NOT an AE or SAE.

SPIROMAC specific expected adverse events:

In this trial the following events are potentially expected:

- Feeling faint or coughing post spirometry

8.3 Procedures for detecting, evaluating recording, & reporting AEs, SAEs

8.3.1 Detecting AEs and SAEs

All AEs and SAEs meeting the criteria for recording within SPIROMAC will be recorded from the time a participant consents to join the trial until the last trial visit. The Investigator will ask about the occurrence of AEs/SAEs at every visit. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence.

8.3.2 Evaluating AEs and SAEs

Depending on severity, when an AE occurs, it is the responsibility of the Investigator (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator (or delegate) should then record all relevant information in the case report form (for AEs) or on the SAE form (for any SAEs).

Information to be collected includes type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.
Seriousness, causality, and expectedness should be evaluated.

Assessment of Seriousness

The Investigator should make an assessment of seriousness, as defined above.

Assessment of Causality (relatedness)

The Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

- **Related**: resulted from administration of any of the research procedures (for this study, use of the NIOX VERO or other study assessments)
- **Unrelated**: where an event is not considered to be related to any of the research procedures (for this study, use of the NIOX VERO or other study assessments.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Expectedness

When assessing expectedness refer to the expected events (Section 6.1).

8.3.3 Reporting AEs and SAEs

Site staff are responsible for notifying the trial office of any AEs and SAEs that require to be recorded in line with the SPIROMAC protocol. To summarise the information above, AEs and SAEs that require to be reported in SPIROMAC are those relating to use of spirometry equipment, the NIOX VERO or other study assessments. An asthma exacerbation is an outcome for this study and is not an AE or SAE. Hospitalisations for treatment planned prior to randomisation, hospitalisation for elective or emergency treatment will not be considered as an AE or SAE.

When an SAE form is uploaded onto the trial website, the Trial Manager will be automatically notified. If, in the opinion of the local PI and the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager will notify the sponsor within 24 hours of receiving the signed SAE notification. The sponsor will provide an

assessment of the SAE. A Sponsor cannot downgrade an assessment from the PI or CI. Any disparity will be resolved by further discussion between these parties.

The CI or delegate will report any related and unexpected SAEs to the REC within 15 days of the CI becoming aware of it. All related SAEs will be summarised and reported to the Ethics Committee, the Funder and the Trial Steering Committee in their regular progress reports.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

9. Sample size and proposed recruitment rate

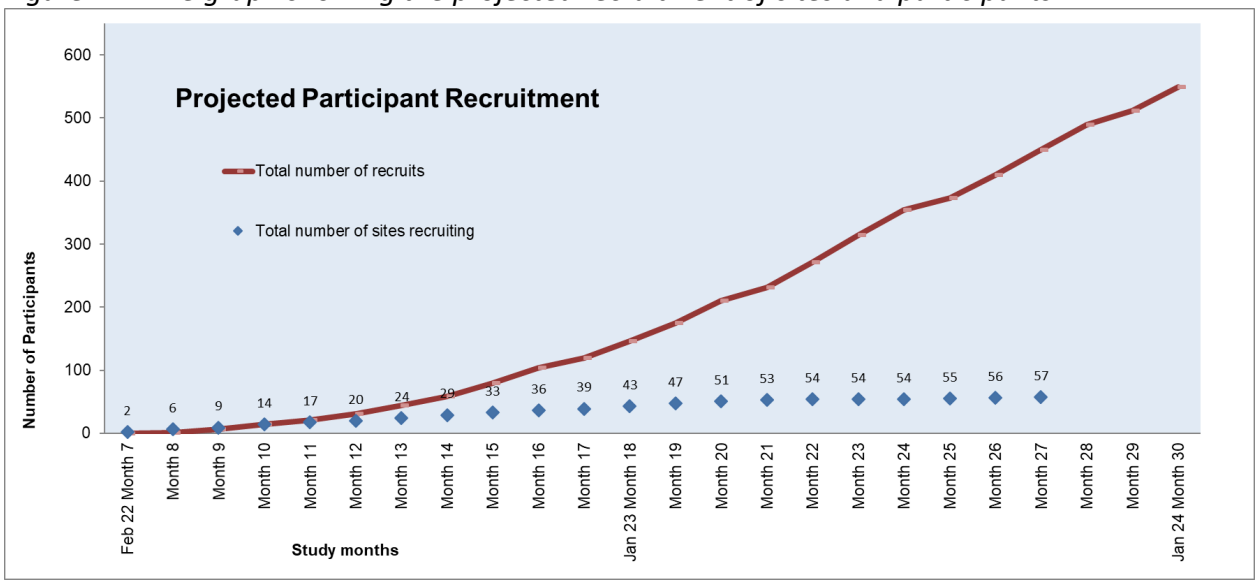
9.1 Sample size

Although our primary outcome (the number of asthma attacks per participant) takes the form of a count variable, we have conservatively based our sample size on the binary outcome of any asthma attack yes/no. We have done this for two reasons: firstly we think that although some children are at risk of multiple attacks within a 12-month period, the majority will have zero or one attack in the time period of follow-up, and we wanted to allow for the scenario where the maximum number of attacks any child has in the trial is one. Secondly, we do not have reasonable estimates of the parameters required for, say, the sample size calculation to compare two negative binomial rates, and calculations are sensitive to values used. Our trial is powered to detect a 28% reduced risk for asthma attacks. We know this magnitude of reduced risk is meaningful to children and their parents/carers. Our observational study found that a reduction of 10% FEV_1 over three months was associated with a 28% increase in the risk for attack over the next three months[16]. This increased risk was independent of age, attack in the previous three months, current asthma control and current medication, and included spirometry measurements within the "normal" range. A 10% reduction is equivalent to one standard deviation for change in %FEV_1 over three months[16]. We know that 55% of children aged 6-15 years attending a secondary care asthma clinic have received ≥1 course of OCS in the previous 12 months[35]. Knowing that outcomes are usually better in clinical trials, we assume an attack proportion of 50% for participants in the control arm and 36% for the intervention arm. Assuming 90% power with 5% significance (2-sided) we need 262 children per group to complete follow up. Allowing for 5% incomplete primary outcome data we will recruit 550 children (i.e. 275 per group).

9.2 Recruitment rates

Figure 2 show the recruitment of sites and participants over time. This projection is based upon 41 secondary care sites recruiting an average of 0.9 participant per month and primary care sites contributing 50 participants over the recruitment phase. Our projection anticipates a slow-down in recruitment during school holidays and takes into account staggered site set up.

Figure 2. A line graph showing the projected recruitment of sites and participants



9.3 Internal pilot study

The nine-month internal pilot phase will start in February 2022 (study month 7) and run to the end of October 2022 (study month 15). The main outcome of the internal pilot study will be the number of participants recruited. Other outcomes[36] will be protocol adherence, equipoise, algorithm feasibility and acceptability, and quality of data. Equipoise will be determined by recruitment rates to the study, observing equal proportions of participants being retained in both arms of the trial and also at three-monthly teleconferences with research teams where we will explore whether some teams/parents are reluctant for some patients to take part in one arm of the SPIROMAC trial. Our work leading up to this application identified that 26 of our RAACENO recruiting centres would recruit for SPIROMAC and where clinical equipoise would not be an issue[15]. The SPIROMAC algorithm will be very similar to that used in RAACENO, and the feasibility and acceptability of the RAACENO algorithm to participants, carers and local clinical teams is currently being formally evaluated. Our experience from RAACENO (where the algorithm had been applied 1577 times at the time of writing) is that it is feasible to use a computer-based algorithm such as we propose to use in SPIROMAC and that its use is acceptable to participants, carers and clinical teams. The feasibility and acceptability of the SPIROMAC algorithm will be evaluated at three-monthly teleconferences with research teams. Quality control will take place during the internal pilot and the entire follow up period to correct missing and anomalous data. Our computer-based case report form will assist the researcher to enter data in the correct format, and within the correct range of values.

Stop/go criteria

During the pilot phase 33 sites will be opened and in accordance with recruitment projections, we expect to randomise 80 participants.

The proposed stop/go criteria (see Table 2) at 9 months, are if we recruit:

- Greater than 72 participants (greater than 90%): We will continue without modification;
- 40 to 72 participants (50% to 90%): We will need to modify recruitment approach, e.g. recruit additional centres, and continue to monitor recruitment carefully to ensure recovery manoeuvres worked.

- Less than 40 (<50%): We will enter discussions with the funder to determine whether the RCT is feasible with the possibility that the trial may need to be terminated.

Table 2. Stop/go criteria

	Red	**Amber**	**Green**
Trial recruitment	<50%	50-90%	>90%
Number of sites opened	<15	15-30	>30
Total number of participants recruited	<40	40-72	>72

9.4 Project timetable and milestones

The funding start date was 1 August 2021, and the study duration is 48 months. Milestones:
Months 1-6: set-up, authorisations
Months 7-30: participant recruitment
Months 10-42: participant follow-up
Months 43-48: data analysis, interpretation of results, report writing and dissemination.

A Gantt chart is shown in appendix 2.

10. Statistical analysis

10.1 Efficacy analysis

The primary outcome (i.e. the number of asthma attacks per participant during the 12-month follow-up) will be analysed using negative binomial regression. The model will adjust for covariates and time in the study as the exposure (this approach allows inclusion of data from participants who do not have follow-up data complete through to 12 months). Covariates to be included are age, gender, socioeconomic status, asthma severity (as evidenced by treatment) and centre (random effect). Secondary outcomes will be analysed in a similar manner using generalized linear models and the appropriate link function. Comparison of PAQLQ at the final assessment (12 months) between treatment groups will be assessed using analysis of covariance, adjusting for covariates listed above and baseline PAQLQ. The participants will be analysed as randomised. The influence of any missing data on the robustness of the findings will be examined using sensitivity analyses incorporating multiple imputation or other relevant strategies under alternative assumptions.

10.2 Mediational analysis

Over the 12-month period we will collect the mechanistic outcomes (FEV_1, FVC and FeNO) at baseline and then every 3 months. We will use casual mediation analysis to explore the indirect effects of treatment mediated by increase in spirometry as measured by FEV_1, FVC or a reduction in eosinophilic airway inflammation as measured by FeNO. We can explore the relationship by using time-to-first-asthma-attack as an outcome in a survival analysis framework and accounting for repeatedly measured FEV_1, FVC and FeNO, which is most likely subject to time-varying confounding, using the methods outlined in Vansteelandt *et al*[37].

All treatment effects will be presented with 95% confidence intervals. We plan only one efficacy and mediation analysis at the end of the trial, there will be no interim analyses for efficacy or futility.

Safety and other data will be adjudicated at least annually by our oversight committees. Analysis will be fully specified in a Statistical Analysis Plan.

11. Organisation: trial management and oversight arrangements

11.1 Trial office in Aberdeen

The Trial Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager takes responsibility for the day to day transaction of trial activities, for example approvals, site set-up and training, oversight of recruitment and follow-up rates etc. The data co-ordinator provides clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal).

The Trial Office team meets formally at least monthly during the course of the trial to ensure smooth running and trouble-shooting.

11.2 Local organisation in sites

The PI and research nurse(s) in each site are responsible for all aspects of local organisation including identifying potential recruits, consenting and assessing participants and completing and maintaining appropriate documentation. Appropriate members of the local team are knowledgeable about the Protocol and will have appropriate Good Clinical Practice (GCP) training if applicable.

If spirometry and/or FeNO measurements are undertaken by a qualified respiratory technician who would be undertaking these measurements within routine clinical practice, (but who are otherwise not involved in the study) GCP training is not mandatory, though we would provide training in completion of the CRF if they were recording the results directly onto the CRF.

A trial-specific delegation log is prepared for each site, detailing the responsibilities of each member of staff working on the trial. The local team is also responsible for notifying SAEs to the Trial Office (see section 8).

11.3 Project Management Group (PMG)

The trial is supervised by its Project management Group (PMG). This consists of the grant holders and representatives from the Trial Office. Observers may be invited to attend at the discretion of the PMG. We will meet/teleconference every 2-3 months on average.

The PMG has the expertise to cover the clinical and methodological aspects of the research.

There will be regular teleconferenced “site meetings”, usually chaired by the CI and attended by research nurses from each centre. Fixed items on the agenda for these

meetings will include recruitment (numbers and challenges), apparatus/equipment (what will need replacing) and problems arising or solved.

There will be a meeting at the end of the study to share the results with investigators.

11.4 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), with independent members, oversees the conduct and progress of the trial. The TSC Charter documents the terms of reference of the TSC, the template for reporting and the names and contact details of members of the TSC. This Charter is filed in the Trial Master File (TMF).

11.5 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) oversees the safety of subjects in the trial. The DMC Charter documents the terms of reference of the DMC and the names and contact details and is filed in the TMF. The committee will meet regularly to monitor the unblinded trial data and serious adverse events and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial.

11.6 Patient and Public Involvement (PPI)

Our co-applicants include Dr Erika Kennington, from the Asthma UK and British Lung Foundation Partnership, and two PPI co-applicants (Mrs Beth Thompson and Mrs Shakeela Riaz). Dr Kennington, Mrs Riaz and Mrs Thompson have been involved in providing insight, comments and guidance in the development of this proposal. Dr Kennington, Mrs Riaz and Mrs Thompson have affirmed the importance of the research question, provided comments on the proposal, and examined our plain English language summary.

Leading up to our stage 2 submission, two meetings with parents of children with asthma have taken place (via Zoom). Discussion at these meetings included the following themes: the adverse experience of asthma attack; the desirability of an objective measurement of control; the acceptability of three-monthly spirometry measurements; having treatment changed by spirometry in the absence of symptoms.

Dr Kennington, Mrs Riaz and Mrs Thompson will be members of the PMG. They will advise the project as part of this team and lead in the preparation of all patient-facing materials. We will actively involve the Aberdeen Young Persons Group (YPG) in the development of the recruitment and data collection materials, study processes, and interpretation of the trial results. We will meet with YPG and we will invite YPG members to join our Patient Advisory panel. The Asthma UK and British Lung Foundation Partnership will create and coordinate a Patient Advisory Panel for our project as well as liaise between the Panel, and the PMG. The Panel's scheduled meetings may coincide with key project meetings (e.g. TSC meetings) in order to enable the group's recommendations to make a change through the TSC. The Asthma UK and British Lung Foundation Partnership will help to identify independent PPI member(s) for the Trial Steering Group. and will liaise with the Patient Advisory Panel group and facilitate communication between the two.

We anticipate dissemination of the trial activity through Asthma UK and British Lung Foundation Partnership at onset and during recruitment, and the trial results on its completion.

Our PPI coordinator will guide the planning, training and facilitation of these activities and enable support for researchers and PPI partners throughout the trial to ensure meaningful and accessible involvement.

12. Research governance, data protection and sponsorship

12.1 Research Governance

CHaRT is a fully registered Clinical Trials Unit with particular expertise in running multicentre RCTs. The trial is run under the auspices of CHaRT based at HSRU, University of Aberdeen. This aids compliance with Research Governance and the principles of GCP, and CHaRT provides centralised trial administration, database support and statistical analyses. CHaRT SOPs are followed.

The CI and Sponsor ensure that adequate systems are in place for monitoring the quality of the trial and that reports are prepared to a level appropriate to the risk assessment of the trial.

The Sponsor's Standard Operating Procedures (SOPs) shall be followed.

12.2 Data protection

Data collected during the study is kept strictly confidential and accessed only by members of the trial team. Data may be looked at by individuals from the Sponsor organisation or NHS sites where it is relevant to the participant taking part in this trial.

The CI and study staff involved with this project will comply with the requirements of the UK General Data Protection Regulations (GDPR) and the Data Protection Act 2018. The HRA recommended wording to fulfil transparency requirements under the UK GDPR for health and care research has been included in the PIL.

The CIs and study staff based in Scotland will also adhere to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via usernames and passwords.

Remote access to the network will be subject to robust authentication, and VPN (Virtual Private Network) connections to the network are only permitted for authorised users, ensuring that use is authenticated, and data is encrypted during transit across the network. No personal data will be downloaded or stored on laptop local hard drives. All data input/access will be via the VPN/secure website.

Published results will not contain any personal data that could allow identification of individual participants.

The CHaRT senior IT development manager (in collaboration with the CI) manages access rights to the data set. Participants are allocated an individual trial number which is used to identify questionnaires and case report forms.

We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses.

12.3 Sponsorship

The University of Aberdeen and Grampian Health Board (NHS Grampian) are the Co-Sponsors for the trial.

13. Ethics and regulatory approvals

The West Midlands – Black Country Research Ethics Committee and any appropriate NHS approvals will be obtained. The trial is conducted according to the principles of GCP provided by Research Governance Guidelines and any appropriate NHS R&D approvals will be obtained. Annual progress reports, end of Trial declaration, and a final report are submitted to the Sponsor and the West Midlands – Black Country REC within the timelines defined in the regulations.

13.1 Protocol compliance and amendment

The Investigators will conduct the trial in compliance with the Protocol given favourable opinion by the West Midlands - Black Country Research Ethics Committee. Any amendment to the Protocol or other approved documents is approved by the Sponsors (and funder if appropriate) before application to REC and R&D, unless in the case of urgent safety measures when the Sponsor is notified as soon as possible. Sponsor will advise if an amendment is substantial / non-substantial and which review bodies need to receive it. Any deviations from the Protocol will be fully documented.

14. Monitoring and audit

The trial is monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of GCP, and all other appropriate regulations. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate to the risk assessment of the trial. Investigators and their host institutions are required to permit trial related monitoring and audits to take place by the Sponsor and/ or regulatory representatives, providing direct access to source data and documents as requested.

14.1 Risk assessment

An independent risk assessment has been carried out by the Sponsor. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate and proportionate to the risk assessment of the study.

15. Finance and insurance

The trial is funded by a grant awarded by the National Institute for Health Research Efficacy and Mechanisms Evaluation (NIHR EME). The necessary trial insurance is provided by the University of Aberdeen.

16. End of trial

The end of follow-up for each participant is defined as the final data capture on that individual. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the Sponsor and REC within 90 days, or 15 days if the trial is terminated prematurely. If terminated prematurely, the Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved, if appropriate.

A summary report of the trial will be provided to the Sponsor and REC within one year of the end of the trial. An end of trial report is also issued to the funders at the end of funding.

17. Data handling, record keeping and archiving

Clinical data is entered into the database by the designated team members working in each recruitment site, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office are entered there. Staff in the Trial Office work closely with local team members to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks further enhance the quality of the data.

Responsibilities for archiving are documented in the <<co-sponsorship / site agreement>>. All essential data and documents (electronic and hard copy) are retained for a period of at least 10 years after close of trial according to the funder requirements and relevant Sponsor and CHaRT archiving SOPs. Electronic data will be archived by the University of Aberdeen.

17.1 Source data

The primary outcome is the number of asthma attacks as reported by the participant (or parent/carer). Many of our secondary outcomes (time to first attack, adverse events, dose of inhaled corticosteroids) are also as reported by the participant (or parent/carer). Asthma control (symptoms) and quality of life are also patient reported.

At baseline and at follow-up, study data can be collected on hard copy case report form or entered directly into the study website.

- If hard copy case report forms are completed, these are considered to be the source document. These will then be entered by the local study team onto the study website.
- If the data is entered directly into the study website, the electronic record is considered to be the source document. In order to maintain a copy of the data that is independent

from the sponsor copy, sites will be encouraged to print or save a copy of the electronic data. The study website will provide this facility.

Each website user will have their own user account and password. These must not be shared. The study website has a full audit trail and every data entry made (or changed) is logged to the specific user.

For all case report forms, there is an electronic record (as part of the study website) which indicates whether the case report form was completed online (no paper copy) or not. This will allow identification of the source document.

Participants will complete questionnaires at baseline and at 3, 6, 9 and 12 month follow-up. The hard copy of these questionnaires will be considered the source document.

18. Satellite studies

It is recognised that the value of the trial may be enhanced by smaller ancillary studies of specific aspects. Plans for these are discussed in advance with the PMG, and if appropriate with the TSC. Depending on the nature of the satellite trial, the Sponsor may consider this to be a non-substantial or a substantial amendment to the REC approval for the SPIROMAC study, or to require REC approval as a project in its own right. R&D management approval may also be required. In such situations, the sponsor will be contacted for advice.

19. Authorship, publication and dissemination

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the PMG and TSC.

Please refer to the Appendix 3 (authorship policy) for full details on authorship.

Once the main trial findings have been published, a lay summary of the findings will be sent to all the families involved in the trial. Trial findings will also be disseminated to professionals involved in the trial, including GPs, PIs at sites, site staff etc.

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Appendix 1: Treatment algorithm: decision trees and treatment steps table

Decision tree - recruitment visit

FINAL NUMBER	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13	R14	R15	R16	R17	R18
C/ACT	>19	>19	>19	>19	>19	>19	>19	13-19	13-19	13-19	13-19	13-19	13-19	13-19	13-19	<13	<13	<13
Adherent	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
AA in last 6 mo	No	No	Yes	Yes	Yes	Yes		No	No	No	No	Yes	Yes	Yes				
Step up in last 3 mo			No	No	No	Yes		No	No	No	Yes	No	Yes	Yes		No	Yes	
SABA	<3d/w	≥3d/w	<3d/w	≥3d/w	≥3d/w			<3d/w	≥3d/w	≥3d/w								
Bud equiv				≤400	>400				≤400	>400			≤400	>400				
CONTROL ARM	No change Path A	RCO[2]	No change Path A	Step up Path B	No change Path A	No change Path A	No change Path A	No change Path C	Step up Path B	No change Path C	No change Path C	Step up Path B	Step up Path B	No change Path C	No change Path C	Step up Path B	RCO[3]	No change Path C
INTERVENTION ARM: Spirometry ratio equal to or above LLN (ie z score ≥ -1.64 "good")	No change Path A	RCO[2]	No change Path A	No change Path A	No change Path A	No change Path A	No change Path A	No change Path C	No change Path C	No change Path C	No change Path C	Step up Path B	No change Path C	No change Path C	No change Path C	Step up Path B	RCO[3]	No change Path C
INTERVENTION ARM: Spirometry ratio below LLN (ie z score < -1.64 "bad")	No change Path A	Step up Path B[1]	No change Path A	Step up Path B[1]	Step up Path B[1]	Step up Path B[1]	No change Path A	Step up Path B	Step up Path B	Step up Path B	Step up Path B	Step up Path B	Step up Path B	Step up Path B	No change Path C	Step up Path B	Step up Path B	No change Path C

Decision tree - path A – follow this path if there was a step down at the previous visit or following *R1/R3/R4/R5/R6/R7 – no change* at baseline

Path A scenario	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16	A17	A18	A19	A20	A21	A22	A23	A24	A25	A26	A27
C/ACT	>19	>19	>19	>19	>19	>19			>19			13-19	13-19	13-19			13-19	13-19	13-19	13-19	13-19	13-19	<13				<13
Adherent	Yes	Yes	Yes	Yes	Yes	Yes			No			Yes	Yes	Yes			Yes	Yes	Yes	Yes	Yes	No	Yes				No
AA in last 3 mo	No	No	Yes	Yes	Yes	Yes						No	No	No			Yes	Yes	Yes	Yes	Yes						
Step up since last visit			No	No	No	Yes						Yes	No	No			Yes	Yes	No	No	No						
SABA	<3d/w	≥3d/w	<3d/w	≥3d/w	≥3d/w								<3d/w	≥3d/w					<3d/w	<3d/w	≥3d/w						
Bud equiv				≤400	>400												≤400	>400	≤400	>400							
CONTROL ARM	Step down Path A	RCO[2]	No change Path C	Step up Path B	No change Path C	No change Path C			No change if adherent at previous visit Path C RCO if second consecutive episode of non-adherence[4]			No change Path C	No change Path C	Step up Path B			Step up Path B	No change Path C	Step up Path B	No change Path C	Step up Path B	No change if adherent at previous visit Path C RCO if second consecutive episode of non-adherence[4]	Step up Path B				No change if adherent at previous visit Path C RCO if second consecutive episode of non-adherence[4]
INTERVENTION ARM: Spirometry change score >-1.6 AND <+1.6 (ie "good" / or stable spirometry)	Step down Path A	RCO[2]	No change Path C	No change Path C	No change Path C	No change Path C			No change if adherent at previous visit Path C RCO if second consecutive episode of non-adherence[4]			No change Path C	No change Path C	No change Path C			No change Path C	No change Path C	No change Path C	No change Path C	Step up Path B	No change if adherent at previous visit Path C RCO if second consecutive episode of non-adherence[4]	Step up Path B				No change if adherent at previous visit Path C RCO if second consecutive episode of non-adherence[4]
INTERVENTION ARM: Spirometry change score ≤ -1.6 OR ≥+1.6 (ie "poor" / or less stable spirometry)	No change Path C	Step up Path B[1]	No change Path C	Step up Path B[1]	Step up Path B[1]	Step up Path B[1]			No change if adherent at previous visit Path C RCO if second consecutive episode of non-adherence[4]			Step up Path B	Step up Path B	Step up Path B			Step up Path B	Step up Path B	Step up Path B	Step up Path B	Step up Path B	No change if adherent at previous visit Path C RCO if second consecutive episode of non-adherence[4]	Step up Path B				No change if adherent at previous visit Path C RCO if second consecutive episode of non-adherence[4]

Decision tree - path B – follow this path if there was a step up at the previous visit

Path B scenario	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15	B16	B17	B18	B19	B20	B21	B22	B23	B24	B25	B26	B27
C/ACT									>19	>19	>19	13-19	13-19		13-19	13-19	13-19	13-19	13-19	13-19	13-19	13-19				<13	
Adherent									No	Yes	Yes	Yes	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	No					
AA in last 3 mo												No	No		No	No	Yes	Yes	Yes	Yes	Yes						
Step up since last visit												Yes	No		No	No	Yes	Yes	No	No	No						
SABA										<3d/w	≥3d/w		<3d/w		≥3d/w	≥3d/w			<3d/w	<3d/w	≥3d/w						
Bud equiv															≤400	>400	≤400	>400	≤400	>400							
CONTROL ARM									No change if adherent at previous visit Path C	No change Path C	RCO[2]	No change Path C	No change Path C		Step up Path B	No change Path C	Step up Path B	No change Path C	Step up Path B	No change Path C	Step up Path B	No change if adherent at previous visit Path C				RCO[3]	
									RCO if second consecutive episode of non-adherence[4]													RCO if second consecutive episode of non-adherence[4]				
INTERVENTION ARM: Spirometry change score >-1.6 AND <+1.6 (ie "good" / or stable spirometry)									No change if adherent at previous visit Path C	No change Path C	RCO[2]	No change Path C	No change Path C		No change Path C	No change Path C	No change Path C	No change Path C	No change Path C	No change Path C	Step up Path B	No change if adherent at previous visit Path C				RCO[3]	
									RCO if second consecutive episode of non-adherence[4]													RCO if second consecutive episode of non-adherence[4]				
INTERVENTION ARM: Spirometry change score ≤ -1.6 OR ≥+1.6 (ie "poor" / or less stable spirometry)									No change if adherent at previous visit Path C	No change Path C	Step up Path B[1]	Step up Path B	Step up Path B		Step up Path B	Step up Path B	Step up Path B	Step up Path B	Step up Path B	Step up Path B	Step up Path B	No change if adherent at previous visit Path C				RCO[3]	
									RCO if second consecutive episode of non-adherence[4]													RCO if second consecutive episode of non-adherence[4]				

Decision tree - path C – follow this path if there was no change at the previous visit (unless previous visit was baseline and the outcome was *R1/R3/R4/R5/R6/R7 – no change* at baseline; these will follow path A)

Path C scenario	C1	C2				C6	C7	C8	C9			C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	C22		C24	C25		C27
C/ACT	>19	>19				>19	>19	>19	>19			13-19	13-19		13-19	13-19	13-19	13-19	13-19	13-19	13-19	13-19		<13	<13		<13
Adherent	yes	yes				Yes	Yes	Yes	No			Yes	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	No		Yes	Yes		No
AA in last 3 mo	No	No				Yes	Yes	Yes				No	No		No	No	Yes	Yes	Yes	Yes	Yes						
Step up since last visit						Yes	No	No				Yes	No		No	No	Yes	Yes	No	No	No			No	Yes		
SABA	<3d/w	≥3d/w											<3d/w		≥3d/w	≥3d/w			<3d/w	<3d/w	≥3d/w						
Bud equiv							≤400	>400							≤400	>400	≤400	>400	≤400	>400							
CONTROL ARM	If previous C/ACT>19 Step down Path A	RCO[3]				No change Path C	Step up Path B	No change Path C	No change if adherent at previous visit Path C			No change Path C	No change Path C		Step up Path B	No change Path C	Step up Path B	No change Path C	Step up Path B	No change Path C	Step up Path B	No change if adherent at previous visit Path C		Step up Path B	RCO[3]		No change if adherent at previous visit Path C
	If previous C/ACT≤19 No change Path C								RCO if second consecutive episode of non-adherence[4]													RCO if second consecutive episode of non-adherence[4]				RCO if second consecutive episode of non-adherence[4]
INTERVENTION ARM: Spirometry change score >-1.6 AND <+1.6 (ie "good" / or stable spirometry)	Step down Path A	RCO[3]				No change Path C	No change Path C	No change Path C	No change if adherent at previous visit Path C			No change Path C	No change Path C		No change Path C	No change Path C	No change Path C	No change Path C	No change Path C	No change Path C	Step up Path B	No change if adherent at previous visit Path C		Step up Path B	RCO[3]		No change if adherent at previous visit Path C
									RCO if second consecutive episode of non-adherence[4]													RCO if second consecutive episode of non-adherence[4]				RCO if second consecutive episode of non-adherence[4]
INTERVENTION ARM: Spirometry change score ≤ -1.6 OR ≥+1.6 (ie "poor" / or less stable spirometry)	No change Path C	Step up Path B[1]				Step up Path B[1]	Step up Path B[1]	Step up Path B[1]	No change if adherent at previous visit Path C			Step up Path B	Step up Path B		Step up Path B	Step up Path B	Step up Path B	Step up Path B	Step up Path B	Step up Path B	Step up Path B	No change if adherent at previous visit Path C		Step up Path B	RCO[3]		No change if adherent at previous visit Path C
									RCO if second consecutive episode of non-adherence[4]													RCO if second consecutive episode of non-adherence[4]				RCO if second consecutive episode of non-adherence[4]

Notes:

Overview of the treatment algorithm (decision trees and treatment step table)

The treatment algorithm comprises the decision trees (above) and the treatment step table (Appendix 2). At the start of each visit, the child will land on a treatment step reflecting their current asthma preventer medication (see Appendix 2). Based on the factors included in the treatment algorithm (C/ACT, adherence, asthma attack, step up, SABA, budesonide equivalent; and, in the intervention arm, spirometry; and at follow-up visits, what happened at the last visit), they will also be placed into one of the above scenarios and the decision tree will make a recommendation as to whether there should a step up, step down or no change to treatment or if the child should be referred for a clinical opinion. The treatment step table will then indicate where the child would step up or step down to.

If children are on a non-standard strength or frequency of inhaler, there is no treatment step for them to land on at the start of a visit. The site will record the inhaler type and select "other strength or frequency of dose". For these children, the treatment algorithm will recommend RCO and will also make a recommendation in terms of step up, step down or no change. However (because there is no landing treatment step), the treatment algorithm cannot make a recommendation as to the preventer medication that the child should take for the next three months.

Application of the decision trees

The location of the information required to apply the decision trees **at baseline** is recorded in the following sections of the case report forms

C/ACT	Total score on Children's Asthma Control Test or Children's Asthma Control Test
Adherent	Adherence to ICS inhaler; Baseline CRF, question C2
AA in last 6 mo	Has there been an asthma attack in the last 6 months; Baseline CRF, question C7
Step up in last 3 mo	Has treatment been stepped up in the last 3 months; Baseline CRF, question C9
SABA	How frequently do they use their SABA inhaler; Baseline CRF, question C4
Bud equiv	What is the dose (as micrograms of budesonide equivalent) of their current ICS inhaler; based on current treatment recorded in the baseline CRF, question C1 (and for calculation of bud equivalent, refer to the treatment step table)
Spirometry	FEV1/FVC ratio in relation to Lower Level of Normal (LLN)

The location of the information required to apply the decision trees in paths A, B and C (i.e. **at follow-up visits)** is recorded in the following sections of the case report forms

C/ACT	Total score on Children's Asthma Control Test or Children's Asthma Control Test
Adherent	Adherence to ICS inhaler; Follow-up CRF, question B4
AA in last 3 mo	Has there been an asthma attack in the last 3 months; Follow-up CRF, question C3
Step up since last visit	Has treatment been stepped up in the last 3 months; Follow-up CRF, question B8a/B8b
SABA	How frequently do they use their SABA inhaler; Baseline CRF, question B6
Bud equiv	What is the dose (as micrograms of budesonide equivalent) of their current ICS inhaler; based on current treatment recorded in the follow-up CRF, question B1 (and for calculation of bud equivalent, refer to the treatment step table)
Spirometry	FEV1 change score in relation to -1.6

At any appointment, if the asthma inhaler technique is "not satisfactory after training" (baseline B4, follow-up A4) the child should be referred for clinical opinion. This rule should be applied before the other factors within the decision tree. The recommendation should NOT include a step up/step down/no change indication. Therefore the recommendation from the treatment algorithm should read: **Refer clinical opinion (RCO) – inhaler technique inadequate after training**.

At any appointment if the child has a separate long acting beta agonist (LABA) inhaler, the child should be referred for clinical opinion (baseline C3, follow-up B5). This rule should be applied before the other factors within the decision tree. The recommendation should include RCO and a recommendation about step up/step down/no change, but will not recommend a specific treatment step. Therefore the recommendation from the treatment algorithm would read: Refer clinical opinion – step up; or Refer clinical opinion – step down; or Refer clinical opinion – no change.

Decision tree path at subsequent visits

At each visit, for most scenarios on the decision trees, the recommendation includes the path that they will follow at the next visit. Please note that a child may be on a different path at each visit. *So for example at baseline they may be recommended no change, path A; at three months they will follow Path A, but may end up with a recommendation at the end of the 3 month visit to Step up, Path B. At the 6 month visit, they will then follow Path B; and so on.*

- *If the decision tree makes a recommendation of step up, step down or no change and the treatment step table can provide the team with a preventer treatment recommendation **and the algorithm is fully followed**, the path indicated in the decision trees above will apply for the subsequent visit. There is also a question on the case report form (baseline N4, follow-up J4) that asks sites to confirm whether there has been a step up, step down or no change in preventer treatment.*

- *If the decision tree makes a recommendation of step up, step down or no change and the treatment step table can provide the team with an inhaler recommendation **but the algorithm is not fully followed**, the sites will confirm in the case report form (baseline N4, follow-up J4) whether there has been a step up, step down or no change. This will inform the path for the subsequent visit. If the clinical opinion was step down, the child will follow path A at the next visit. If the clinical opinion was step up, the child will follow path B at the next visit. If the clinical opinion was no change, the child will follow path C at the next visit.*

- *If the decision tree makes a recommendation of **refer clinical opinion** or the treatment step tables indicates **refer clinical opinion**, the asthma team will make a decision to step up, step down or make no change to treatment. The research team at site will record this on the case report form (baseline N4, follow-up J4). In these situations, the clinical opinion to step up, step down or make no change to treatment will determine the path for the next visit. If the clinical opinion was step down, the child will follow path A at the next visit. If the clinical opinion was step up, the child will follow path B at the next visit. If the clinical opinion was no change, the child will follow path C at the next visit.*

Specific footnotes for the decision trees.

[1] These children (R2, R4, R5, R6, A2, A4, A5, A6, B11, C2, C6, C7, C8) should be flagged because only one step up during the trial in these scenarios is permitted. If they land on one of these scenarios for a second (or subsequent) time, the recommendation would be "No Change" and they would follow Path C at the next appointment.

[2] Children who receive an RCO from the decision tree because they are well controlled/frequent SABA use. The recommendation should NOT include a step up/step down/no change indication. Therefore the recommendation from the treatment algorithm should read: **Refer Clinical Opinion (RCO) – well controlled asthma, but frequent use of SABA.**

[3] Children who receive an RCO from the treatment algorithm because of poor asthma control. The recommendation should NOT include a step up/step down/no change indication. Therefore the recommendation from the treatment algorithm should read: **Refer Clinical Opinion (RCO) – poor asthma control.**

[4] Children who receive an RCO from the treatment algorithm because this is their second consecutive episode of non-adherence. The recommendation should NOT include a step up/step down/no change indication. Therefore the recommendation from the treatment algorithm should read: **Refer Clinical Opinion (RCO) – second consecutive episode of poor adherence to treatment.**

TREATMENT STEPS

				INTERVENTION ARM: At baseline: Intermediate/poor control (C/ACT <19) and Spirometry ratio below LLN (ie z score < -1.64 "bad")[4]. At follow-up: Intermediate /poor control (C/ACT<19) and spirometry change score ≤-1.6 OR ≥+1.6 [3]	**STANDARD CARE ARM** (all scenarios) **INTERVENTION ARM** (all scenarios apart from those indicated in previous column)			
Asthma medication (ICS/LABA/LTRA)[1]	**Budesonide equivalent; L (LABA)**	**BTS Step[2]**	**Drug no**	Age<12, Age ≥12 years	Age <12 years		Age ≥12 years	
				Step up[4]	Step up[4]	Step down[4]	Step up[4]	Step down[4]
SABA only (no inhaled corticosteroid)	0	1	**0**		2	n/a	2	n/a
SABA only (no inhaled corticosteroid) plus LTRA	0	2	**1**		4	0	4	0
Beclomethasone (Clenil) 50 mcg MDI 2 puffs twice daily	200	2	**2**		3	0	3	0
Beclomethasone (Clenil) 100 mcg MDI 2 puffs twice daily	400	2/3[5]	**3**		34	2	34	2
Beclomethasone (Clenil) 50 mcg MDI 2 puffs twice daily plus LTRA	200	3	**4**		5	2	5	2
Beclomethasone (Clenil) 100 mcg MDI 2 puffs twice daily plus LTRA	400	3	**5**		37	3	37	3
Budesonide (Pulmicort Turbohaler) 100 mcg DPI 1 dose twice daily	200	2	**6**	40	7	0	7	0
Budesonide (Pulmicort Turbohaler) 200 mcg DPI 1 dose twice daily	400	2/3[5]	**7**		41	6	41	6
Budesonide (Pulmicort Turbohaler) 400 mcg DPI 1 dose twice daily	800	3/4[6]	**8**		42	7	42	7
Budesonide (Pulmicort Turbohaler) 100 mcg DPI 1 dose twice daily plus LTRA	200	3	**9**	43	10	6	10	6

				INTERVENTION ARM: At baseline: Intermediate/poor control (C/ACT <19) and Spirometry ratio below LLN (ie z score < -1.64 "bad")[4]. At follow-up: Intermediate /poor control (C/ACT<19) and spirometry change score ≤-1.6 OR ≥+1.6 [3]	**STANDARD CARE ARM** (all scenarios) **INTERVENTION ARM** (all scenarios apart from those indicated in previous column)			
Asthma medication (ICS/LABA/LTRA)[1]	**Budesonide equivalent; L (LABA)**	**BTS Step[2]**	**Drug no**	Age<12, Age ≥12 years	Age <12 years		Age ≥12 years	
				Step up[4]	Step up[4]	Step down[4]	Step up[4]	Step down[4]
Budesonide (Pulmicort Turbohaler) 200 mcg DPI 1 dose twice daily plus LTRA	400	3	**10**		44	7	44	7
Budesonide (Pulmicort Turbohaler) 400 mcg DPI 1 dose twice daily plus LTRA	800	4	**11**		45	10	45	10
Fluticasone (Flixotide Accuhaler) 50 mcg DPI 1 dose twice daily	200	2	**12**		13	0	13	0
Fluticasone (Flixotide Accuhaler) 100 mcg DPI 1 dose twice daily	400	2/3[5]	**13**		28	12	28	12
Fluticasone (Flixotide Accuhaler) 250 mcg DPI 1 dose twice daily	1000	3/4[6]	**14**		29	13	29	13
Fluticasone (Flixotide Accuhaler) 500 mcg DPI 1 dose twice daily	2000	5	**15**		A	A	30	14
Fluticasone (Flixotide Accuhaler) 50 mcg DPI 1 dose twice daily plus LTRA	200	3	**16**		17	12	17	12
Fluticasone (Flixotide Accuhaler) 100 mcg DPI 1 dose twice daily plus LTRA	400	3	**17**		31	13	31	13
Fluticasone (Flixotide Accuhaler) 250 mcg DPI 1 dose twice daily plus LTRA	1000	4	**18**		32	17	32	17
Fluticasone (Flixotide Accuhaler) 500 mcg DPI 1 dose twice daily plus LTRA	2000	5	**19**		A	A	33	18
Fluticasone (Flixotide Evohaler) 50 mcg MDI 1 puff twice daily	200	2	**20**		21	0	21	0
Fluticasone (Flixotide Evohaler) 50 mcg MDI 2 puffs twice daily	400	2/3[5]	**21**		34	20	34	20

				INTERVENTION ARM: At baseline: Intermediate/poor control (C/ACT <19) and Spirometry ratio below LLN (ie z score < -1.64 "bad")[4]. At follow-up: Intermediate /poor control (C/ACT<19) and spirometry change score ≤-1.6 OR ≥+1.6 [3]	**STANDARD CARE ARM** (all scenarios) **INTERVENTION ARM** (all scenarios apart from those indicated in previous column)			
Asthma medication (ICS/LABA/LTRA)[1]	**Budesonide equivalent; L (LABA)**	**BTS Step[2]**	**Drug no**	Age<12, Age ≥12 years	Age <12 years		Age ≥12 years	
				Step up[4]	Step up[4]	Step down[4]	Step up[4]	Step down[4]
Fluticasone (Flixotide Evohaler) 125 mcg MDI 2 puffs twice daily	1000	3/4[6]	**22**		35	21	35	21
Fluticasone (Flixotide Evohaler) 250 mcg MDI 2 puffs twice daily	2000	5	**23**		A	A	36	22
Fluticasone (Flixotide Evohaler) 50 mcg MDI 1 puff twice daily plus LTRA	200	3	**24**		25	20	25	20
Fluticasone (Flixotide Evohaler) 50 mcg MDI 2 puffs twice daily plus LTRA	400	3	**25**		37	21	37	21
Fluticasone (Flixotide Evohaler) 125 mcg MDI 2 puffs twice daily plus LTRA	1000	4	**26**		38	25	38	25
Fluticasone (Flixotide Evohaler) 250 mcg MDI 2 puffs twice daily plus LTRA	2000	5	**27**		A	A	39	26
Seretide Accuhaler 100 1 dose twice daily	400 L	3	**28**		31	13	31	13
Seretide Accuhaler 250 1 dose twice daily	1000 L	4	**29**		32	28	32	28
Seretide Accuhaler 500 1 dose twice daily	2000 L	5	**30**		A	A	33	29
Seretide Accuhaler 100 1 dose twice daily plus LTRA	400 L	3	**31**		32	28	32	28
Seretide Accuhaler 250 1 dose twice daily plus LTRA	1000 L	4	**32**		38	31	33	31
Seretide Accuhaler 500 1 dose twice daily plus LTRA	2000 L	5	**33**		A	A	39	32

				INTERVENTION ARM: At baseline: Intermediate/poor control (C/ACT <19) and Spirometry ratio below LLN (ie z score < -1.64 "bad")[4]. At follow-up: Intermediate /poor control (C/ACT<19) and spirometry change score ≤-1.6 OR ≥+1.6 [3]	**STANDARD CARE ARM** (all scenarios) **INTERVENTION ARM** (all scenarios apart from those indicated in previous column)			
Asthma medication (ICS/LABA/LTRA)[1]	**Budesonide equivalent; L (LABA)**	**BTS Step[2]**	**Drug no**	Age<12, Age ≥12 years	Age <12 years		Age ≥12 years	
				Step up[4]	Step up[4]	Step down[4]	Step up[4]	Step down[4]
Seretide Evohaler 50/25 MDI 2 puffs twice daily	400 L	3	**34**		37	21	37	21
Seretide Evohaler 125/25 MDI 2 puffs twice daily	1000 L	4	**35**		38	34	38	34
Seretide Evohaler 250/25 MDI 2 puffs twice daily	2000 L	5	**36**		A	A	39	35
Seretide Evohaler 50/25 MDI 2 puffs twice daily plus LTRA	400 L	3	**37**		38	34	38	34
Seretide Evohaler 125/25 MDI 2 puffs twice daily plus LTRA	1000 L	4	**38**		RCO	37	39	37
Seretide Evohaler 250/25 MDI 2 puffs twice daily plus LTRA	2000 L	5	**39**		A	A	RCO	38
Symbicort Turbohaler 100/6 I dose twice daily[7]	200 L	3	**40**		41	6	41	6
Symbicort Turbohaler 200/6 DPI 1 dose twice daily[7]	400 L	3	**41**		44	7	44	7
Symbicort Turbohaler 400/12 DPI 1 dose twice daily[7]	800 L	4	**42**		45	41	45	41
Symbicort Turbohaler 100/6 I dose twice daily plus LTRA[7]	200 L	3	**43**		44	40	44	40
Symbicort Turbohaler 200/6 DPI 1 dose twice daily plus LTRA[7]	400 L	3	**44**		45	41	45	41
Symbicort Turbohaler 400/12 DPI 1 dose twice daily plus LTRA[7]	800 L	4	**45**		38	44	39	44

				INTERVENTION ARM: At baseline: Intermediate/poor control (C/ACT <19) and Spirometry ratio below LLN (ie z score < -1.64 "bad")[4]. At follow-up: Intermediate /poor control (C/ACT<19) and spirometry change score ≤-1.6 OR ≥+1.6 [3]	**STANDARD CARE ARM** (all scenarios) **INTERVENTION ARM** (all scenarios apart from those indicated in previous column)			
Asthma medication (ICS/LABA/LTRA)[1]	**Budesonide equivalent; L (LABA)**	**BTS Step[2]**	**Drug no**	Age<12, Age ≥12 years	Age <12 years		Age ≥12 years	
				Step up[4]	Step up[4]	Step down[4]	Step up[4]	Step down[4]
Qvar 50 Autohaler or Aerosol MDI 1 puff twice a day	200	2	**47**		48	0	48	0
Qvar 100 Autohaler or Aerosol MDI 1 puff twice a day	400	2/3[5]	**48**		34	47	34	47
Qvar 100 Autohaler or Aerosol MDI 2 puffs twice a day	800	3/4[6]	**49**		35	48	35	48
Qvar 100 Autohaler or Aerosol MDI 4 puffs twice a day	1600	5	**50**		A	A	36	49
Qvar 50 Autohaler or Aerosol MDI 1 puff twice a day plus LTRA	200	3	**51**		52	47	52	47
Qvar 100 Autohaler or Aerosol MDI 1 puff twice a day plus LTRA	400	3	**52**		37	48	37	48
Qvar 100 Autohaler or Aerosol MDI 2 puffs twice a day plus LTRA	800	4	**53**		38	52	38	52
Qvar 100 Autohaler or Aerosol MDI 4 puffs twice a day plus LTRA	1600	5	**54**		A	A	39	53
Asmabec clickhaler 50 1 dose once daily	100	2	**55**		56	0	56	0
Asmabec clickhaler 50 1 dose twice daily	200	2	**56**		57	55	57	55
Asmabec clickhaler 100 1 dose twice daily	400	2/3[5]	**57**		34	56	34	56
Asmabec clickhaler 250 1 dose twice daily	1000	3/4[6]	**58**		35	57	35	57

				INTERVENTION ARM: At baseline: Intermediate/poor control (C/ACT <19) and Spirometry ratio below LLN (ie z score < -1.64 "bad")[4]. At follow-up: Intermediate /poor control (C/ACT<19) and spirometry change score ≤-1.6 OR ≥+1.6 [3]	**STANDARD CARE ARM** (all scenarios) **INTERVENTION ARM** (all scenarios apart from those indicated in previous column)			
Asthma medication (ICS/LABA/LTRA)[1]	**Budesonide equivalent; L (LABA)**	**BTS Step[2]**	**Drug no**	Age<12, Age ≥12 years	Age <12 years		Age ≥12 years	
				Step up[4]	Step up[4]	Step down[4]	Step up[4]	Step down[4]
Asmabec clickhaler 50 1 dose once daily plus LTRA	100	3	**59**		60	55	60	55
Asmabec clickhaler 50 1 dose twice daily plus LTRA	200	3	**60**		61	56	61	56
Asmabec clickhaler 100 1 dose twice daily plus LTRA	400	3	**61**		37	57	37	57
Asmabec clickhaler 250 1 dose twice daily plus LTRA	1000	4	**62**		38	61	38	61
Budelin Novolizer 200 1 dose once daily	200	2	**63**		64	0	64	0
Budelin Novolizer 200 1 dose twice daily	400	2/3[5]	**64**		34	63	34	63
Budelin Novolizer 200 2 doses twice daily	800	3/4[6]	**65**		35	64	35	64
Budelin Novolizer 400 1 dose once daily	400	2/3[5]	**66**		34	63	34	63
Budelin Novolizer 400 1 dose twice daily	800	3/4[6]	**67**		35	66	35	66
Budelin Novolizer 400 2 doses twice daily	1600	5	**68**		A	A	36	67
Budelin Novolizer 200 1 dose once daily plus LTRA	200	3	**69**		70	63	70	63
Budelin Novolizer 200 1 dose twice daily plus LTRA	400	3	**70**		37	64	37	64

				INTERVENTION ARM: At baseline: Intermediate/poor control (C/ACT <19) and Spirometry ratio below LLN (ie z score < -1.64 "bad")[4]. At follow-up: Intermediate /poor control (C/ACT<19) and spirometry change score ≤-1.6 OR ≥+1.6 [3]	**STANDARD CARE ARM** (all scenarios) **INTERVENTION ARM** (all scenarios apart from those indicated in previous column)			
Asthma medication (ICS/LABA/LTRA)[1]	**Budesonide equivalent; L (LABA)**	**BTS Step[2]**	**Drug no**	Age<12, Age ≥12 years	Age <12 years		Age ≥12 years	
				Step up[4]	Step up[4]	Step down[4]	Step up[4]	Step down[4]
Budelin Novolizer 200 2 doses twice daily plus LTRA	800	4	**71**		38	70	38	70
Budelin Novolizer 400 1 dose once daily plus LTRA	400	3	**72**		37	66	37	66
Budelin Novolizer 400 1 dose twice daily plus LTRA	800	4	**73**		38	72	38	72
Budelin Novolizer 400 2 doses twice daily plus LTRA	1600	5	**74**		A	A	39	73
Asmanex Twisthaler 200 mcg 1 dose once daily	400	2/3[5]	**75**		34	2	34	2
Asmanex Twisthaler 200 mcg 1 dose twice daily	800	3/4[6]	**76**		35	75	35	75
Asmanex Twisthaler 200 mcg 2 dose twice daily	1600	5	**77**		A	A	36	76
Asmanex Twisthaler 400 mcg 1 dose twice daily	1600	5	**78**		A	A	36	76
Asmanex Twisthaler 200 mcg 1 dose once daily plus LTRA	400	3	**79**		37	75	37	75
Asmanex Twisthaler 200 mcg 1 dose twice daily plus LTRA	800	4	**80**		38	79	38	79
Asmanex Twisthaler 200 mcg 2 dose twice daily plus LTRA	1600	5	**81**		A	A	39	80
Asmanex Twisthaler 400 mcg 1 dose twice daily plus LTRA	1600	5	**82**		A	A	39	80

				INTERVENTION ARM: At baseline: Intermediate/poor control (C/ACT <19) and Spirometry ratio below LLN (ie z score < -1.64 "bad")[4]. At follow-up: Intermediate /poor control (C/ACT<19) and spirometry change score ≤-1.6 OR ≥+1.6 [3]	**STANDARD CARE ARM** (all scenarios) **INTERVENTION ARM** (all scenarios apart from those indicated in previous column)			
Asthma medication (ICS/LABA/LTRA)[1]	**Budesonide equivalent; L (LABA)**	**BTS Step[2]**	**Drug no**	Age<12, Age ≥12 years	Age <12 years		Age ≥12 years	
				Step up[4]	Step up[4]	Step down[4]	Step up[4]	Step down[4]
Relvar Ellipta 92/22 one dose once a day	200 L	3	**83**		84	2	84	2
Relvar Ellipta 184/22 one dose once a day	400 L	3	**84**		86	3	86	3
Relvar Ellipta 92/22 one dose once a day plus LTRA	200 L	3	**85**		86	83	86	83
Relvar Ellipta 184/22 one dose once a day plus LTRA	400 L	3	**86**		38	84	38	84
Flutiform 50/5 mcg MDI inhaler or K-haler one puff twice daily	200 L	3	**87**		88	2	88	2
Flutiform 50/5 mcg MDI inhaler or K-haler two puff twice daily	400 L	3	**88**		92	3	92	3
Flutiform 125/5 mcg MDI inhaler or K-haler one puff twice daily	500 L	4	**89**		93	3	93	3
Flutiform 125/5 mcg MDI inhaler or K-haler two puff twice daily	1000 L	4	**90**		94	89	94	89
Flutiform 50/5 mcg MDI inhaler or K-halerone puff twice daily plus LTRA	200 L	3	**91**		92	87	92	87
Flutiform 50/5 mcg MDI inhaler or K-haler two puff twice daily plus LTRA	400 L	3	**92**		94	88	94	88
Flutiform 125/5 mcg MDI inhaler or K-haler one puff twice daily plus LTRA	500 L	4	**93**		94	89	94	89
Flutiform 125/5 mcg MDI inhaler or K-haler two puff twice daily plus LTRA	1000 L	4	**94**		RCO	93	39	93

				INTERVENTION ARM: At baseline: Intermediate/poor control (C/ACT <19) and Spirometry ratio below LLN (ie z score < -1.64 "bad")[4]. At follow-up: Intermediate /poor control (C/ACT<19) and spirometry change score ≤-1.6 OR ≥+1.6 [3]	**STANDARD CARE ARM** (all scenarios) **INTERVENTION ARM** (all scenarios apart from those indicated in previous column)			
Asthma medication (ICS/LABA/LTRA)[1]	**Budesonide equivalent; L (LABA)**	**BTS Step[2]**	**Drug no**	Age<12, Age ≥12 years	Age <12 years		Age ≥12 years	
				Step up[4]	Step up[4]	Step down[4]	Step up[4]	Step down[4]
Alvesco 80 mcg MDI one puff once daily	160	2	**95**		96	0	96	0
Alvesco 80 mcg MDI two puffs once daily	320	2/3[5]	**96**		34	95	34	95
Alvesco 160 mcg MDI one puff once daily	320	2	**97**		34	95	34	95
Alvesco 160 mcg MDI two puffs once daily	640	3/4[6]	**98**		34	97	34	97
Alvesco 160 mcg MDI two puffs twice daily	1280	5	**99**		A	A	35	98
Alvesco 80 mcg MDI one puff once daily plus LTRA	160	3	**100**		101	95	101	95
Alvesco 80 mcg MDI two puffs once daily plus LTRA	320	3	**101**		37	96	37	96
Alvesco 160 mcg MDI one puff once daily plus LTRA	320	3	**102**		37	97	37	97
Alvesco 160 mcg MDI two puffs once daily plus LTRA	640	4	**103**		37	102	37	102
Alvesco 160 mcg MDI two puffs twice daily plus LTRA	1280	5	**104**		A	A	38	103

Abbreviations: mcg - microgram
A – children aged <12 years who are on this medication at baseline would not be eligible for the study.

n/a – children on SABA only cannot step down further; if the decision tree indicates step down; there will be no change to their treatment step (ie they will remain on SABA only until a step up is indicated by the decision tree)

RCO – refer for clinical opinion. If the decision tree indicates step up; the child will be referred to see the asthma doctor.

Footnotes:

[1] The drugs included in the treatment step table are based on table 13 of the 2019 BTS guidelines. A number of the drugs listed in the guideline are not included on the algorithm because they are not licensed for use in children (eg Fostair). If new drugs/devices become available during the study period, these will be considered for inclusion on the treatment algorithm if (i) they are licensed for children; and (ii) they are appropriate given the step up/down rules listed below.

Children who are taking a dose other than stated in the table are eligible for the study; and if there is not an appropriate landing step for them, the algorithm will return a "refer clinical opinion" outcome.

[2] BTS step is based on the BTS 2019 guidelines, and uses the following general rules:

	Age <12 years	Aged ≥12 years
100 to 200 bud equivalent no LABA or LTRA	Step 2	Step 2
201 to 400 bud equivalent no LABA or LTRA	Step 3	Step 2
401 to 1000 bud equivalent no LABA or LTRA[a]	Step 4	Step 3
1001 to 2000 bud equivalent no LABA or LTRA	Not eligible	Step 5[b]
100 to 400 bud equivalent with LABA and/or LTRA	Step 3	Step 3
401 to 1000 bud equivalent with LABA and/or LTRA	Step 4	Step 4
1001 to 2000 bud equivalent with LABA and/or LTRA	Not eligible	Step 5

In the BTS 2019 guidelines 401-800 bud equivalent as monotherapy is not mentioned; on the basis of clinical experience, we are suggesting the classification in the table. Step 5 in the BTS 2019 guidelines states "refer patient for specialist care", in practice the specialist will introduce ICS at doses of 801 to 2000 budesonide equivalent and this is how we have included in the above classification. If there are any children who join the study on SABA only (no ICS) but taking LTRA, these will be classified as BTS step 2. Children who are on SABA only at baseline will be classified as BTS step 1.

[3] In the intervention arm, for children with poor asthma control on low-dose ICS and reduced spirometry the algorithm will (where possible) introduce LABA treatment rather than increasing the ICS to 400 mcg bud equivalent. This pertains to step up decisions in the INTERVENTION arm only (scenarios R8, R9, R10, R11, R12, R13, R14, R16, R17, A12, A13, A14, A17, A18, A19, A20, A21, A23 B12, B13, B15, B16, B17, B18, B19, B20, B21, C12, C13, C15, C16, C17, C18, C19, C20, C21, C24). The treatment recommendation only differs in respect to drug numbers 7 and 10. All other treatment recommendations will be identical to those shown in the final four columns of the above table.

[4] General rules for step up/step down

Step up - children aged <12

- Increase ICS to 400 mcg bud equivalent per day
- Add LABA
- Add LTRA
- Increase ICS to 800/1000 mcg bud equivalent per day

Step up - children aged ≥12

- Increase ICS to 400 mcg bud equivalent per day
- Add LABA
- Add LTRA
- Increase ICS to 2000 mcg bud equivalent per day

Step down (all ages)

- Reduce ICS to 400 mcg bud equivalent per day
- Remove LTRA
- Remove LABA
- Reduce ICS further

When increasing/decreasing ICS, the steps are: 200 bud equivalent per day; 400/500 bud equivalent per day; 800/1000 bud equivalent per day, 2000 bud equivalent per day. Children who step down from 200 bud equivalent per day will be on SABA only.

Where possible, delivery device should be maintained. In general, step up with the same inhaler device where possible. If the maximum dose is reached on a dry powder device and step up is still required, switch to MDI device. Therefore, when the maximum (for age) dose of ICS is reached on the Accuhaler device and both LABA and LTRA have been added, the delivery device should be changed to an Evohaler device (with spacer) at the same dose.

Children aged >=12 years who step up from Symbicort Turbohaler 400/12 DPI 1 dose twice daily (800 mcg bud equiv) will step up to Seretide Evohaler 250/25 MDI/spacer 2 puffs twice daily (2000 mcg bud equiv).

Additional rules for step up/step down

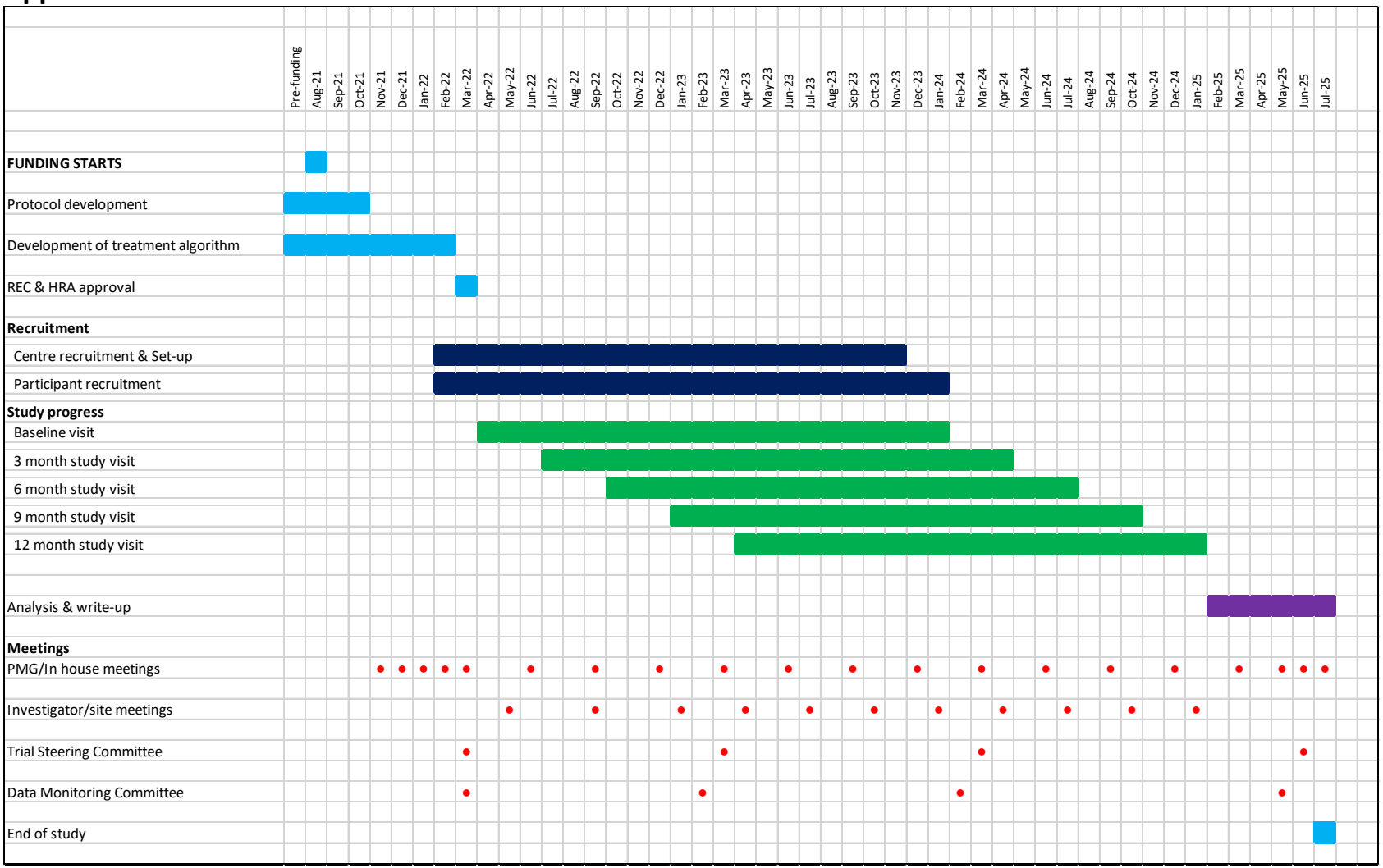
- Flutiform 125/5 mcg MDI inhaler or K-haler one puff twice daily (budesonide equivalent 500L; drug 89); for step down treat as 400L so step down to 400
- Alvesco 80 mcg MDI two puffs once daily (budesonide equivalent 320; drug 96); for step up treat as 400 budesonide equivalent, so step up to 400L
- Alvesco 160 mcg MDI one puff once daily (budesonide equivalent 320; drug 97); for step up treat as 400 budesonide equivalent, so step up to 400L
- Alvesco 160 mcg MDI two puffs once daily (budesonide equivalent 640; drug 98); for step up treat as 400 budesonide equivalent, so step up to 400L
- Alvesco 160 mcg MDI two puffs twice daily (budesonide equivalent 1280; drug 99); for step up treat as 1000 budesonide equivalent, so step up to 1000L

[5] BTS step differs depending on age of child. For those aged >=12 years, BTS step is 2; for those aged <12 years, BTS step is 3.

[6] BTS step differs depending on age of child. For those aged >=12 years, BTS step is 3; for those aged <12 years, BTS step is 4.

[7] Symbicort Turbohaler is licensed for MART therapy. If children join the study on MART, their strength/frequency of the Symbicort Turbohaler will be recorded as “other” and the recommendation will be RCO.

Appendix 2. GANTT chart



Note: this GANTT chart reflects the current funding agreement

Appendix 3: Authorship Policy for the SPIROMAC trial

1. DEFINING AUTHORSHIP

Authorship of published or presented papers is based on the following criteria[1]:

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
ii. Drafting the work or revising it critically for important intellectual content; AND
iii. Final approval of the version to be published; AND
iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

2. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals[2,3] and are in accordance with the rules of the International Committee of Medical Journal Editors (ICMJE)[1].

All contributors must fulfil the criteria detailed in section 1: DEFINING AUTHORSHIP in order to qualify for authorship.

Contributors who meet fewer than all four of the criteria for authorship listed above should not be listed as authors, but they should be acknowledged. For example, participation solely in the acquisition of funding, collection of data or technical editing, language editing or proofreading the article is insufficient by itself to justify authorship[1]. Those persons may be acknowledged and their contribution described. See section 3: ACKNOWLEDGEMENTS.

a. Preferred CHaRT authorship

Where possible, all CHaRT trials should publish using all the named contributors who qualify for authorship in the byline i.e. Jane Doe, John Doe, John Smith and Ann Other.

However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstance, group authorship may be appropriate using bylines similar to “The XXXXX trial group” or “Jane Doe, John Doe, John Smith, Ann Other and the XXXX trial group”. The article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. For some journals the journal will provide instructions on how to ensure the names of the collaborators appear on PubMed or equivalent.

Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group')[2]. Again, the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

b. Determining authorship

These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion numbers (ii) or (iii). Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript[1].

Tentative decisions on authorship should be made as early as possible[3]. These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Trial Steering Committee (TSC).

c. Ordering of authors

The following rules may help with the ordering of authors, particularly for publications with individual authorship:

i. The person who has taken the lead in writing may be the first author.
ii. The senior author may wish to be the last named author.
iii. Those who have made a major contribution to analysis or writing (i.e. have done more than commenting in detail on successive drafts) may follow the first author immediately; where there is a clear difference in the size of these contributions, this should be reflected in the order of these authors.
iv. All others who fulfil the four authorship criteria described in Section 1: DEFINING AUTHORSHIP may complete the list in alphabetical order of their surnames.

3. ACKNOWLEDGEMENTS

All those who make a contribution to a publication, but who do not fulfil the criteria for authorship, such as interviewers, data processors, staff at the recruiting sites, secretaries and funding bodies, should be acknowledged by name, usually in an 'Acknowledgements' section specifying their contributions. Because acknowledgment may imply endorsement by acknowledged individuals of a trial's data and conclusions, authors are advised to obtain written permission to be acknowledged from all acknowledged individuals[1].

4. DISCLAIMERS

All papers arising from CHaRT must include the full title of the Health Services Research Unit (HSRU) and the appropriate disclaimer specified by the Chief Scientist Office (CSO). For the current disclaimer please see Q-Pulse.

Authors should also ensure they include the trial funder's disclaimer: refer to the funders website for details. Be aware that other disclaimers may also be required.

5. QUALITY ASSURANCE

Ensuring quality assurance is essential to the good name of the trial group. All reports of work arising from the SPIROMAC trial, including conference abstracts, outputs describing methodological aspects of the trial, and any outputs describing results from the trial, should be peer reviewed by the Project Management Group. The Project Management Group will be responsible for decisions about submission following internal peer review. Submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. If individual members of the group are dissatisfied by decisions, the matter may be referred to the TSC.

It is hoped that the adoption and dissemination of this policy will prevent disputes that cannot be resolved by informal discussion. However, any member of the trial team with a concern about authorship should discuss it with the relevant Chief Investigator, TSC, Line Manager or Programme Director as appropriate.

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