Protocol

A proof-of-concept single group study of an anti-inflammatory reliever therapy stepwise approach to the pharmacological treatment of adult asthma

Short title	AIR Algorithm Study
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Chief Investigator Signature

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Funder, the Investigator Team and members of the Research Ethics Committee, unless authorised to do so.

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2. SYNOPSIS

Trial Title	A proof-of-concept single group study of an anti-inflammatory reliever therapy stepwise approach to the pharmacological treatment of adult asthma
Internal ref. no.	AIR Algorithm Study
Clinical Phase	Phase 3
Trial Design	Prospective, single-centre, open label, single group study
Trial Participants	Participants aged 18-75 with asthma, currently taking SABA reliever monotherapy, ICS plus SABA reliever therapy, or ICS/LABA plus SABA reliever therapy
Sample Size	100
Treatment Duration	The trial will be conducted in two phases, with a total duration of 52 weeks: Phase One: Week 0 to Week 26 Phase Two: Week 26 to Week 52
Follow Up Duration	Nil
Planned Trial Period	Recruitment period: 26 weeks Treatment period: 52 weeks Total trial period: 78 weeks

	Objectives	**Outcome Measures**
Primary	To assess participant satisfaction with the AIR stepwise approach to the pharmacological treatment of adult asthma	• Phase One: TSQM v.II Global Satisfaction score at Week 26 • Phase Two: TSQM v.II Global Satisfaction score at Week 52
Key Secondary	To assess participant satisfaction with the AIR stepwise approach to the pharmacological treatment of adult asthma	• Estimate the minimal clinically important difference (MCID) for each domain of the TSQM • Participant preference scores
	To assess participant beliefs about medicines used in the AIR stepwise approach to the pharmacological treatment of adult asthma	• BMQ-AIR and BMQ-SABA scores at Weeks 26 and 52
	To assess participant flow through the AIR stepwise approach to the pharmacological treatment of asthma	• Proportion of participants on each treatment step • Proportion of participants that change treatment step

	To assess the effectiveness of the AIR stepwise approach to the pharmacological treatment of adult asthma	• ACT, ACQ-5 and AQLQ-S scores at Weeks 26 and 52 • Number and rate of severe exacerbations • Number and rate of moderate and severe exacerbations • On treatment FEV_1 at Weeks 26 and 52 • FeNO at Weeks 26 and 52
	To assess patterns of medication use with the AIR stepwise approach to the pharmacological treatment of adult asthma	• Difference in participant reported inhaler use and monitor recorded use • Mean ICS dose per day
	To assess the safety of the AIR stepwise approach to the pharmacological treatment of adult asthma	• Adverse event in the 52-week trial period • Serious adverse event in the 52-week trial period
Nested Sub-studies	AIR Tutorial Sub-study (AIR T) AIR Qualitative Sub-study (AIR Q)	
Investigational Medicinal Product	The medicinal product dispensed during the treatment period is an approved medication for the treatment of asthma. Participants will be assigned the AIR stepwise approach to the management of asthma, in which a combined budesonide/formoterol (Symbicort) turbuhaler is used as required for relief of symptoms ± budesonide/formoterol (Symbicort) used twice daily as maintenance therapy. The total daily dose of budesonide/formoterol (Symbicort) will be adjusted throughout the trial in accordance with a participant's reported use and whether they have experienced an asthma exacerbation.	
Formulation and Dose	Budesonide/formoterol (Symbicort) Turbuhaler 200/6µg per actuation	
Route of Administration	All medications dispensed during the trial will be administered by inhalation.	

3. ABBREVIATIONS AND DEFINITIONS

ACT	Asthma Control Test
ACQ	Asthma Control Questionnaire
AE	Adverse Event
AIR	Anti-Inflammatory Reliever
AQLQ-S	Asthma Quality of Life Questionnaire with Standardised Activities
AR	Adverse Reaction
ATS	American Thoracic Society
BMQ-AIR	Beliefs about Medicines Questionnaire – Anti-Inflammatory Reliever
BMQ-SABA	Beliefs about Medicines Questionnaire – Short-Acting Beta-Agonist
CI	Chief Investigator
eCRF	Electronic Case Report Form
ED	Emergency Department
ERS	European Respiratory Society
DSMC	Data and Safety Monitoring Committee
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume over 1 second
FVC	FVC Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GP	General Practitioner
HDEC	Health and Disability Ethics Committee
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
IMP	Investigational Medicinal Product
LABA	Long-Acting Beta-Agonist
MRINZ	Medical Research Institute of New Zealand
NHI	National Health Index
NZ	New Zealand
PI	Principal Investigator
PIS-CF	Participant Information Sheet-Consent Form
REDCAP	Research Electronic Data Capture
SABA	Short-Acting Beta-Agonist
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMART	Single Maintenance And Reliever Therapy
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSQM	Treatment Satisfaction Questionnaire for Medication

Moderate Exacerbation of Asthma

A moderate asthma exacerbation is defined by any of the following criteria:

a) Worsening asthma resulting in unplanned medical review (primary care or ED visit) but not severe enough to warrant systemic corticosteroid use, such as a course of oral prednisone, and/or hospital admission, or

b) Worsening asthma resulting in the use of systemic corticosteroids for fewer than 3 days

Severe Exacerbation of Asthma

A severe asthma exacerbation is defined as per the ATS/ERS guidelines:[1]

a) The use of systemic corticosteroids for at least 3 days because of asthma, or

b) Hospitalisation or emergency department (ED) visit because of asthma, requiring systemic corticosteroids

In addition to the ATS/ERS guidance the AIR Algorithm Study will also include:

c) Worsening asthma resulting in unplanned medical review (primary care or ED visit) severe enough to warrant an acute prescription of systemic corticosteroid, such as a course of prednisone

For an exacerbation to be counted as a separate event, it must be preceded by at least 7 days during which neither of the above criteria are fulfilled.

Asthma Attack

An Asthma Attack is defined as a deterioration in asthma symptoms severe enough to warrant the use or prescription of systemic corticosteroids, such as a course of prednisone.

High Use of Inhaler

>8 actuations of budesonide/formoterol 200/6µg in a 24-hour period.

This threshold is based on the limits of beta agonist use requiring medical review defined by the self-management plans promoted by the Asthma and Respiratory Foundation of New Zealand.[2]

Marked Overuse of Inhaler

>12 actuations of budesonide/formoterol 200/6µg in a 24-hour period.

This threshold is based on the limits of formoterol use within a 24-hour period recommended in the Symbicort datasheet.

24-hour Period

From midnight to midnight, at local time to the investigator site.

Scheduled Study Visit

This refers to any of the 5 pre-defined study visits as outlined in Section 8 and Appendix B: Schedule of Procedures.

Unscheduled Study Visit

This refers to any visit arranged in addition to the scheduled visits and takes place outside of scheduled visit windows as outlined in Section 8.8.

End of Trial

The end of trial is the date of the last visit of the last participant.

Unapproved Medicines

Any new medicines that have not been granted consent for distribution by the Minister of Health. 'Unapproved medicines' include new chemical or biological entities and new dosage forms and new strengths of approved medicines, and a different, unapproved formulation of an approved medicine.

4. BACKGROUND AND RATIONALE

There is substantive evidence that ICS/formoterol used as Anti-Inflammatory Reliever therapy (AIR) is superior to short acting beta agonist (SABA) reliever therapy in reducing severe exacerbation risk across the spectrum of asthma severity, from intermittent/mild to severe disease. This evidence now forms the basis of the 2019 GINA Update in which ICS/formoterol reliever therapy is recommended as the preferred reliever therapy for all treatment steps.[8] There is therefore a need to study a practical algorithm for the stepwise approach to the treatment of asthma utilising ICS/formoterol reliever therapy with and without maintenance ICS/formoterol therapy, across the spectrum of disease severity.

An algorithm based on such a regimen is likely to have greater efficacy, reduced systemic steroid related adverse effects, and similar airways anti-inflammatory activity, be more cost-effective and represent the patient's preferred regimen, compared with the traditional GINA mandated stepwise approach to the pharmacological treatment of asthma utilising SABA reliever therapy.[9] For this fundamental change in practice to occur we propose the use of the AIR Algorithm, a practical stepwise treatment incorporating ICS/formoterol reliever with and without ICS/formoterol maintenance therapy.[10] The AIR Algorithm is based on the combination budesonide/formoterol (Symbicort) turbuhaler due to the extensive evidence of its efficacy and safety across the range of adult asthma severity.

This is a proof-of-concept single group study that seeks to provide an initial comprehensive assessment of the AIR Algorithm. This study aims to establish participant satisfaction with the AIR therapy stepwise approach to the pharmacological treatment of adult asthma. The primary outcome variable is the Global Satisfaction score of the Treatment Satisfaction Questionnaire for Medication (TSQM v.II), a validated measure of patient satisfaction across a range of chronic conditions.[11] The TSQM v.II consists of 11 questions representing 4 domains (medication effectiveness, associated side effects, convenience and global satisfaction), each scored from 0 to 100, higher scores indicating greater levels of satisfaction. This outcome measure has been chosen as participant satisfaction provides an assessment of the acceptability of the AIR algorithm and highlights the importance of patient satisfaction in the approach to asthma management, with patient satisfaction shown to be associated with higher levels of treatment adherence and improved asthma control.[12] The study will also provide a preliminary assessment of the efficacy and safety of the AIR algorithm, as well as describe patterns of medication use and participant engagement with this novel regimen.

5. OBJECTIVES AND OUTCOME MEASURES

The trial will be conducted in two phases: Phase One will take place between Visit 1 to Visit 3 (Week 1 to Week 26) and Phase Two between Visit 3 and Visit 5 (Week 26 to Week 52).

5.1. Outcome Measures at Completion of Phase One

Objectives	Outcome Measures	Timepoint(s) of evaluation
Primary Objective		
To assess participant satisfaction with the AIR stepwise approach to the pharmacological treatment of adult asthma	• Visit 3 TSQM Globall Satisfaction Score	Week 26
Secondary Objectives		
To assess participant satisfaction with the AIR stepwise approach to the pharmacological treatment of adult asthma	• The minimal clinically important difference (MCID) for the Global Satisfaction domain of the TSQM	Week 26
	• Individual scores for each domain of the TSQM (effectiveness, convenience, side effects, global satisfaction)	Week 13 & 26
	• Participant preference scores	Week 26
To assess participant flow through the AIR stepwise approach to the pharmacological treatment of asthma	• Number of participants on each treatment step	Week 13 & 26
	• Number of participants that change treatment step	Week 13 & 26
To assess the effectiveness of the AIR stepwise approach to the pharmacological treatment of adult asthma	• Visit 3 ACT Score	Week 26
	• Visit 3 ACQ-5 Score	Week 26
	• Visit 3 AQLQ-S Score	Week 26
	• Visit 3 On-treatment FEV_1	Week 26
	• Visit 3 FeNO	Week 26
	• Number and rate of severe exacerbations	Week 26
	• Number and rate of moderate and severe exacerbations	Week 26
	• Proportion of participants withdrawn and treatment discontinued and reason	Week 26
To assess patterns of medication use with the AIR stepwise approach to the pharmacological treatment of adult asthma	• Difference between participant reported inhaler use and electronic monitor recorded use*	Week 13 & 26
	• Mean ICS dose per day (budesonide µg/day)*	Week 13 & 26
	• Mean β-agonist dose per day (formoterol µg/day)*	Week 13 & 26
	• Proportion of participants requiring other asthma related medications	Week 13 & 26
	• Longest duration of no actuations (days)*	Week 13 & 26
	• Proportion of days of no inhaler use*	Week 13 & 26
	• Number of days of high inhaler use*	Week 13 & 26
	• Proportion of high inhaler use episodes without medical review within 48 hours	Week 13 & 26
	• Number of days of marked inhaler overuse*	Week 13 & 26

	• Proportion of marked inhaler overuse episodes without medical review within 48 hours	Week 13 & 26
To assess the safety of the AIR stepwise approach to the pharmacological treatment of adult asthma	• Adverse events • Proportion with at least 1 related AE • Serious adverse events • Proportion with at least 1 related SAE	Week 26 Week 26 Week 26 Week 26
To assess participant beliefs about medicines used in the AIR stepwise approach to the pharmacological treatment of adult asthma	• Visit 3 BMQ-AIR scores (Necessities and Concerns) • Visit 3 BMQ-SABA scores (Necessities and Concerns)	Week 26 Week 26

5.2. Outcome Measures at Completion of Phase Two

Objectives	Outcome Measures	Timepoint(s) of evaluation
Primary Objective		
To assess participant satisfaction with the AIR stepwise approach to the pharmacological treatment of adult asthma	• Visit 5 TSQM Global Satisfaction Score	Week 52
Secondary Objectives		
To assess participant satisfaction with the AIR stepwise approach to the pharmacological treatment of adult asthma	• Individual scores for each domain of the TSQM (effectiveness, convenience, side effects, global satisfaction) • Participant preference scores	Week 39 & 52 Week 52
To assess participant flow through the AIR stepwise approach to the pharmacological treatment of asthma	• Number of participants on each treatment step • Number of participants that change treatment step • Self-reported number of times participant changed treatment step • Proportion of participants that qualified for a treatment step change • Proportion of participants that qualified for a treatment step change and declined • Participant led treatment step changes +/- 14 days of an asthma attack	Week 39 & 52 Week 39 & 52 Week 39 & 52 Week 52 Week 52 Week 52
To assess the effectiveness of the AIR stepwise approach to the pharmacological treatment of adult asthma	• Visit 5 ACT Score • Visit 5 ACQ-5 Score • Visit 5 AQLQ-S Score • Visit 5 On-treatment FEV_1 • Visit 5 FeNO	Week 52 Week 52 Week 52 Week 52 Week 52

	• Number and rate of severe exacerbations	Week 52
	• Number and rate of moderate and severe exacerbations	Week 52
	• Proportion of participants withdrawn and treatment discontinued and reason	Week 52
To assess patterns of medication use with the AIR stepwise approach to the pharmacological treatment of adult asthma	• Difference between participant reported inhaler use and electronic monitor recorded use*	Week 39 & 52
	• Mean ICS dose per day (budesonide µg/day)*	Week 39 & 52
	• Mean β-agonist dose per day (formoterol µg/day)*	Week 39 & 52
	• Proportion of participants requiring other asthma related medications	Week 39 & 52
	• Longest duration of no actuations (days)*	Week 39 & 52
	• Proportion of days of no inhaler use*	Week 39 & 52
	• Number of days of high inhaler use*	Week 39 & 52
	• Proportion of high inhaler use episodes without medical review within 48 hours	Week 39 & 52
	• Number of days of marked inhaler overuse*	Week 39 & 52
	• Proportion of marked inhaler overuse episodes without medical review within 48 hours	Week 39 & 52
To assess the safety of the AIR stepwise approach to the pharmacological treatment of adult asthma	• Adverse event	Week 52
	• Proportion with at least 1 related AE	Week 52
	• Serious adverse event	Week 52
	• Proportion with at least 1 related SAE	Week 52
To assess participant beliefs about medicines used in the AIR stepwise approach to the pharmacological treatment of adult asthma	• Visit 5 BMQ SABA score (Necessities and Concerns)	Week 52
	• Visit 5 BMQ AIR score (Necessities and Concerns)	Week 52
To assess the carbon footprint of the AIR stepwise approach to the pharmacological treatment of adult asthma	• Carbon footprint as carbon dioxide-equivalent (CO_2e) emissions per person year	Week 52

*NOTE: This data is collected from electronic monitors only, not participant report.

For further details on the AIR Tutorial and AIR Qualitative sub-study objectives and outcome measures see separate sub-study protocols.

6. TRIAL DESIGN

This is a prospective, single centre, interventional, open label, single group study of a novel asthma treatment algorithm (APPENDIX A: Figure 1) in 100 patients diagnosed with asthma aged 18-75 years, who prior to enrolment have been prescribed SABA reliever therapy alone, maintenance ICS plus SABA reliever

therapy, or maintenance ICS/LABA plus SABA reliever therapy. There will be 25 participants recruited from each of the four GINA treatment steps i.e. 100 participants in total.

Participants will be assessed for eligibility and allocated to the treatment regimen at Visit 1 (week 1). Participants will be reviewed every 13 weeks and followed up for a total of one year. The one-year follow up period will be undertaken in two phases; in Phase One participants will be followed for 26 weeks with clinic mandated changes in treatment steps, according to the AIR Algorithm (table 2a-2c); in Phase Two participants will be followed for a further 26 weeks, with any changes in treatment between Week 26 and Week 52 made by the participant in accordance with the AIR Algorithm (Appendix D: Figure 13; page 3). From Week 26 to 39 participants will be asked to review their treatment monthly. Between Week 39 and 52 participants will be encouraged to adjust their treatment as often as they feel necessary.

7. PARTICIPANT IDENTIFICATION

7.1. Inclusion Criteria

- Self-reported doctor's diagnosis of asthma
- Age 18 to 75 years
- Current use (within the last 12 months) of either:
    - SABA reliever monotherapy
    - ICS maintenance plus SABA reliever therapy
    - ICS/LABA maintenance plus SABA reliever therapy
- Participant is willing and able to give informed consent for participation in the trial
- In the Investigator's opinion, participant is able and willing to comply with all trial requirements
- Participant is willing to allow their General Practitioner and/or consultant, if appropriate, to be notified of participation in the trial

7.2. Exclusion Criteria

- Current use (within last 3 months) of other asthma medications including:
    - Budesonide/Formoterol Single Maintenance and Reliever Therapy (SMART)
    - Leukotriene receptor antagonists
    - Long acting muscarinic antagonists
    - Theophylline
    - Regular oral corticosteroids
    - Sodium cromoglycate or nedocromil sodium
    - Monoclonal antibody therapy
- Self-reported urgent medical review for asthma, or treatment with systemic corticosteroids such as oral prednisone, in the two weeks before potential study entry.
- ICU admission for asthma (ever).

- Self-reported diagnosis of COPD, bronchiectasis, vocal cord dysfunction or interstitial lung disease.
- Self-reported greater than 20 pack year smoking history, or onset of respiratory symptoms after the age of 40 years in current or ex-smokers with ≥10 pack year history.
- Self-reported current pregnancy or breast feeding at the time of enrolment or planned pregnancy within the study period.
- Self-reported congestive heart failure, atrial fibrillation, unstable coronary artery disease, or other clinically significant cardiac disease.
- Participant is unwilling or unable to switch from current asthma treatment regimen.
- Self-report of participation in another research trial involving an unapproved investigational medicinal product, in the past 3 months (see Section 3 for definition of 'Unapproved Medicines').
- A Body Mass Index of ≥40
- Any known or suspected contraindications to the medications prescribed for the study or their respective excipients.
- Any other condition which, at the Investigator's discretion, is believed may present a safety risk or impact the feasibility of the study or the study results.

8. TRIAL PROCEDURES

Trial Procedures will be conducted as follows and are summarised in Appendix B: Schedule of Procedures.

8.1. Recruitment

Potential participants will be identified from clinical trial unit databases, General Practitioners (GPs) and direct advertising (including via social media). If interested, potential participants will be provided with a Participant Information Sheet and Consent Form (PIS-CF). Once an appropriate amount of time has been given for the participant to consider the information, they will be contacted again by a Study Investigator to discuss attending an initial screening visit. Participants will be encouraged to discuss the PIS and their involvement in the study with family, whānau and their healthcare provider, prior to signing the consent form.

8.2. Informed Consent

The participant (or their legal representative) must personally complete (sign and date, including electronic completion) the latest approved version of the PIS-CF before any trial specific procedures are performed.

Written and verbal versions of the PIS-CF will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate

in the trial. Written Informed Consent will then be obtained by means of participant dated signature (including e-signature, where applicable) and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site.

8.3. Screening, Eligibility and Baseline Assessments

Potential participants will attend for a screening visit, at which eligibility will be assessed. Those who do not meet the eligibility criteria will not proceed to enrolment, and if the participant is deemed ineligible, then a reason for this will be recorded. Where possible, the screening and enrolment visit will occur on the same day.

8.3.1. Medical History and Demographics

The following medical history and demographic data will be collected at the screening visit:

- Date of birth, age, gender, ethnicity
- Contact details (address, phone number, email)
- GP contact details
- National Health Index (NHI). The NHI number will be entered into the eCRF and used by the MRINZ to centrally validate exacerbation outcome data.
- Height and weight
- Asthma history
    - Age of diagnosis
    - Current medications for asthma including dose
    - Whether the participant is currently prescribed a systemic corticosteroid rescue pack, including dose and number of days per course
    - Whether the participant currently uses an asthma action plan, and whether it is with or without peak flow measurement (if currently using action plan incorporating peak flow measurement, recent best peak flow measurement should be recorded on individual action plans)
    - Number of unplanned medical reviews for a deterioration in asthma symptoms in the past 12 months that did not warrant the use of systemic corticosteroids
    - Number of courses of systemic corticosteroids and number of days per course in the past 12 months
    - Number of ED visits and hospital admissions for asthma in the last 12 months for which a systemic corticosteroid was prescribed
- All other medical conditions and medications
- Smoking history: smoking status (ex, current, never) and pack years
- Females with child bearing potential only: self-reported pregnancy status

8.3.2. Treatment Satisfaction Questionnaire for Medication (TSQM)[11]

The TSQM (V.II) will be administered in accordance with the TSQM user guide at Visit 1.

8.3.3. Beliefs about Medicines Questionnaire - Anti-Inflammatory Reliever (BMQ-AIR)

The BMQ-AIR will be administered in accordance with the user guide at Visit 1.

8.3.4. Beliefs about Medicines Questionnaire – Short-Acting Beta-Agonist (BMQ-SABA)

The BMQ-SABA will be administered in accordance with the user guide at Visit 1.

8.3.5. Asthma Control Test Questionnaire (ACT)[13]

The ACT will be administered in accordance with the ACT user guide at Visit 1.

8.3.6. Asthma Control Questionnaire (ACQ-5)[14]

The ACQ-5 will be administered in accordance with the ACQ-5 user guide at Visit 1.

8.3.7. Asthma Quality of Life with Standardised activities (AQLQ-S) Questionnaire[15]

The AQLQ-S will be administered in accordance with the AQLQ-S user guide at Visit 1.

8.3.8. Fractional exhaled Nitric Oxide (FeNO)

FeNO will be measured using a FeNObreath® device (made by Bedfont Scientific, United Kingdom), in accordance with guidelines published by the ATS 2005[16] and MRINZ infection control operating procedures. Participants will not be required to withhold any medication or abstain from eating or drinking, prior to the measurement being taken. FeNO will be obtained prior to spirometry being performed.

8.3.9. Spirometry

Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) will be measured in accordance with ATS/ERS 2015 criteria[17] and MRINZ infection control operating procedures, using an NND Easy-on PC Spirometer. Participants will not be required to withhold any medication or abstain from eating or drinking, prior to the measurements being performed.

8.3.10. Smoking Cessation Advice

The Investigator will provide the participant with the Quitline pamphlet and advice regarding smoking cessation where applicable.

8.4. Treatment Allocation

Following the screening process, eligible participants who have given written informed consent to be enrolled in the study will be allocated the AIR stepwise approach to the management of asthma.

8.4.1. Determination of Treatment Step at Enrolment

This will be a standardised and automated algorithm undertaken as part of the enrolment process. The system will allocate treatment to the participant based on their current prescribed treatment regimen based on the GINA (2018) criteria (APPENDIX A: Figure 2 and 3) as summarised in Table 1. The Investigator will be provided with the appropriate entry step to the AIR treatment regimen.

Table 1: Determination of Treatment Step at Enrolment

Treatment pre-enrolment	AIR Algorithm Step at enrolment
GINA Step 1: SABA monotherapy	**Allocate to Step 1:** ICS/LABA reliever: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) one actuation as required to relieve symptoms
GINA Step 2: Low dose ICS plus SABA reliever	**Allocate to Step 2:** low dose ICS/LABA: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) one actuation twice daily **and** ICS/LABA reliever: budesonide/formoterol 200µg/6µg one actuation as required to relieve symptoms
GINA Step 3: Medium or high dose ICS plus SABA reliever **or** Low dose ICS/LABA plus SABA reliever	
GINA Step 4: Medium or high dose ICS/LABA plus SABA reliever	**Allocate to Step 3:** medium dose ICS/LABA: budesonide/ formoterol 200µg/6µg Turbuhaler (Symbicort) two actuations twice daily **and** ICS/LABA reliever: budesonide/formoterol 200µg/6µg one actuation as required to relieve symptoms

8.4.2. Provision of Asthma Action Plan

All participants will receive training on inhaler technique, with a demonstration using dummy inhalers, written instructions, and inspiratory flow training. Inhaler technique will be reassessed at subsequent visits. An asthma action plan will be provided to all participants, based on their treatment. The action plans will be modified versions of the self-management plans promoted by the Asthma and Respiratory Foundation of New Zealand.[2] The purpose of providing these plans is to both reinforce the treatment regimen and provide written instructions on what actions the participants should take in the situation of worsening asthma, in particular when to seek GP review and emergency medical care.

Participants will not be required to measure their peak flow or to fill in a record card every day as this would prompt the participants to take their medicines regularly and promote adherence. Those subjects who already monitor their peak flows on entry to the study however may continue to do so with an action plan incorporating peak flow use. For the purpose of this study, a drop in peak flow to <60% of recent best will signify a deterioration in asthma control, requiring contact with a doctor. A drop in peak flow to <40% of recent best will signify an asthma emergency requiring urgent contact with emergency services. Participants will be advised that they remain under the usual care of their GP for the duration of the study.

8.4.3. Educational Material

All participants will have a Study Investigator explain the concepts behind the AIR Algorithm and when to seek medical help. Half the participants will also be presented with an interactive educational tutorial. Participants will be randomised in equal proportions to either receive the interactive tutorial or not.

All participants will have their understanding of the explanations provided evaluated with a simple knowledge questionnaire. Participants allocated to the interactive tutorial group will receive feedback from the questionnaire as part of the tutorial design. Participants not randomised to the interactive tutorial group will not receive specific feedback based on their questionnaire results. All participants will be allocated time to raise any further questions with the Study Investigator. For further detail see AIR Tutorial sub-study protocol.

8.4.4. Asthma Diary Card / MyCap Mobile App

An asthma diary card will be provided for the purpose of the participant documenting unplanned medical visits, details of courses of prednisone and other changes in asthma medications/ treatment. An electronic form of the diary card will also be available, known as MyCap mobile app. MyCap is a mobile extension of secure electronic data capture tool REDCap which can be installed on participants' mobile devices. This allows secure self-reported data entry and syncs directly with their research record. Participants will be able to log unplanned medical visits, courses of prednisone and other changes in asthma treatment.

8.4.5. Medication Dispensing

At Visit 1 all participants will be issued with 3 to 5 new Symbicort Turbuhalers (depending on treatment step) and will be informed that all dispensed inhalers (including used or empty inhalers) are to be brought to their next study visit. They will be asked to stop using their current inhalers following Visit 1 and to store them somewhere securely at home, dispose of them safely, or hand them to the Investigator.

Participants will be advised not to use other non-study inhalers or nebulisers unless indicated by their doctor. If they do use non-study inhalers or nebulisers they will be asked to document the date, time and dose. Participants will be advised to contact the Investigator if there are concerns the allocated inhalers are not operating correctly or that they will run out of inhaler medications prior to the next study visit.

8.4.6. Electronic Monitors and Pre-dispensing Monitor Checks

An electronic monitor will be incorporated in each turbuhaler (Symbicort) device. Participants will be informed that they are using a modified inhaler that has been produced specifically to count the precise number and timing of doses used during the study period. They will be informed that monitors are not to be removed, tampered with or gotten wet and that monitors will record if they have been tampered with. Monitors must be tested after enrolment and prior to dispensing (see Section 10 for further details).

8.5. Visit Two (Week 13), Three (Week 26), Four (Week 39) and Five (Week 52) Assessments

Participants will attend the study site clinic at each visit, as summarised in Appendix B: Schedule of Procedures. Study visits are to be scheduled to occur within ±7 days of their due date. If this is not possible for some reason or they have to be held early or postponed the visit window may be extended at the investigator's discretion. Scheduled study visits will be postponed to ensure participants do not attend visits if they are experiencing any respiratory or flu-like symptoms, and to allow a minimum of 2 weeks from a self-reported urgent medical review or treatment with systemic steroids for asthma. Participants

will be contacted prior to their scheduled study appointments to confirm attendance and to ensure the participant is in good health prior to the visit. If a participant fails to attend their scheduled visits at the study clinic they will be contacted by telephone and arrangements made to reschedule the missed appointment.

The following assessments/ procedures will be performed at scheduled study visits:

8.5.1. Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM(V.II) will be administered in accordance with the TSQM user guide at each scheduled study visit and in the case of an unscheduled study visit for the purpose of treatment discontinuation or study withdrawal.

8.5.2. Beliefs about Medicines Questionnaire - Anti-Inflammatory Reliever (BMQ-AIR)

The BMQ-AIR will be administered as per baseline at Visit 3 and Visit 5 only.

8.5.3. Beliefs about Medicines Questionnaire – Short-Acting Beta-Agonist (BMQ-SABA)

The BMQ-SABA will be administered as per baseline at Visit 3 and Visit 5 only.

8.5.4. Asthma Control Test Questionnaire (ACT)

The ACT questionnaire will be administered as per baseline at Visit 3 and Visit 5 only.

8.5.5. Asthma Control Questionnaire (ACQ-5)

The ACQ-5 will be administered as per baseline at Visit 3 and Visit 5 only.

8.5.6. Asthma Quality of Life with Standardised Activities Questionnaire (AQLQ-S)

The AQLQ-S will be administered as per baseline at Visit 3 and Visit 5 only.

8.5.7. Participant Management Preference Question

The MRINZ Participant Management Preference Question (Appendix C: Figure 11) will be administered at Visit 3 and Visit 5 only. The question will be self-completed by the participant.

8.5.8. Fractional Exhaled Nitric Oxide (FeNO)

FeNO will be measured as per Section 8.3.8. at Visit 3 and Visit 5 only.

8.5.9. Spirometry

Spirometry will be conducted as per Section 8.3.9. at Visit 3 and Visit 5 only.

8.5.10. Asthma Exacerbation Review

The Investigator will record if the participant has experienced a moderate and/or severe exacerbation since the previous visit. Asthma history data since the last visit will be collected by participant self-report and from review of Diary Cards (Appendix D) and MyCap mobile app data.

Specific enquiry and documentation required for assessment of asthma exacerbations including:

- Any medical review (GP/ED/hospitalisation)
- Any systemic corticosteroids such as oral prednisone taken and duration of course
- Any non-study inhaled drugs taken
- Any change in medication
- Any concerns with equipment use (including monitors and inhalers)

The participant's GP should be contacted when required, for example to confirm an unscheduled medical visit date or details of medications prescribed, should the participant not be able to provide the necessary data by self-report.

8.5.11. Adverse Event Review

The Investigator will ask the participant about any adverse events experienced since the previous visit. These will be recorded in accordance with Section 11.

8.5.12. Medication Review

The Investigator will ask the participant about any changes to their medication since the previous visit. The Investigator will also ask the participant how many times they have used their Symbicort inhaler, both as reliever (PRN) and preventer, over the past week, on average per week over the past one month, and on average per week over the past three months. Participants will be asked to confirm what treatment step of the AIR algorithm they are on. This will be recorded in the source documents.

If participants self-report high use (>8 puffs budesonide/formoterol Turbuhaler in 24-hour period) without medical review in the past 7 days, they will be advised to seek medical review from their GP or usual healthcare provider, in accordance with their action plan. If it is apparent that there may be difficulty obtaining such a medical review in a timely manner, then the Investigator may consider issuing a 5-day prescription for prednisone and advise participants to seek urgent medical review if their symptoms do not improve. If the Investigator concludes that the participant requires urgent medical assessment and treatment, then they will refer to the appropriate After Hours/ED service.

If a healthcare provider makes a change to the study allocated treatment not in keeping with the AIR algorithm, the Investigator will review whether it is in the patient's best interests to withdraw from the study or revert back to the study allocated treatment. Should the participant revert back to the study allocated treatment, the Investigator will review whether the participant warrants treatment modification as per the AIR Algorithm (table 2a-2c).

8.6. Treatment Modification Post Enrolment

For the first 26 weeks, during Phase One, participants will be followed with clinic mandated changes in treatment steps, according to the AIR Algorithm (table 2a-2c); in Phase Two participants will be followed for a further 26 weeks, with any changes in treatment between Week 26 and Week 52 made by the participant in accordance with the AIR Algorithm. From Week 26 to Week 39 participants will be asked to review their treatment monthly. Between Week 39 and Week 52 participants will be encouraged to adjust their treatment as often as they feel necessary.

8.6.1. Determination of Treatment Step Post Enrolment during Phase One

At Visit 2 and 3, the amount of Symbicort reliever used per week on average over the past 3 months and whether the participant has experienced an asthma attack (defined in section 3), as reported by the participant, will determine whether the participant either remains on the same step of the treatment pathway, is 'stepped-up' to the next level or 'stepped-down' to the preceding level in accordance with the AIR Algorithm (Tables 2a-2c).

This will be a standardised and automated algorithm undertaken to allocate treatment to the participant. The Investigator will be provided with the appropriate treatment step to the AIR treatment regimen. The Investigator will review the output to ensure it is correct, and issue an action plan for the applicable treatment regimen.

Participants that experience an asthma attack between Visit 1 and Visit 3 will be advised to contact the Investigator to arrange an urgent unscheduled visit to review their allocated treatment and ensure the participant is "stepped up" to the next treatment level.

In the AIR Algorithm, Step 1 (PRN ICS/formoterol) represents the lowest level of treatment whilst Step 3 represents the highest level of treatment. Participants who meet the criteria to be stepped up beyond Step 3 of the AIR Algorithm during the 12-month period will be referred for specialist review at the completion of the study.

8.6.2. Determination of Treatment Step during Phase Two

At Visit 3 participants will be given a Phase Two Action Plan which will provide instructions explaining how to change their treatment step according to frequency of medication use and occurrence of asthma attacks. Between Visit 3 and Visit 5 participants will be encouraged to self-adjust their treatment in accordance with the AIR Algorithm clearly explained in their asthma action plans (Appendix D). From Week 26 to Week 39 participants will be asked to review their treatment monthly. Between Week 39 and Week 52 participants will be encouraged to adjust their treatment as often as they feel necessary. Changes to treatment may also be made by the primary care physician.

At Visit 5 the Investigator will assess and, if necessary, adjust the allocated treatment to ensure each participant completes the study on the correct AIR Algorithm treatment level.

8.6.3. Review of Asthma Action Plan

At each visit participants will be given further education on medication use and inhaler technique. An Asthma Action Plan specific to their determined treatment step (Table 2a-2c) will be provided at Visit 2. At Visit 3 all participants will be provided with an Asthma Action Plan that explains how to use the AIR stepwise approach to asthma management. At Visit 3 and Visit 4 participants will be encouraged to self-adjust their own treatment steps as required.

Participants will be reminded that they should remain under the usual care of their GP for the duration of the study.

Table 2a: Phase One AIR Algorithm Treatment Decisions Step 1

Current Treatment Step	Assessment	Treatment to be Issued
AIR Step 1: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) one actuation as required to relieve symptoms	Reliever therapy use, on average over last 3 months ≤7 actuations per week and no asthma attack since last visit	**Remain on the same step (Step 1)**; ICS/LABA reliever: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) one actuation as required to relieve symptoms
	Reliever therapy use, on average over last 3 months ≤7 actuations per week and ≥1 asthma attack since last visit **or** Reliever therapy use, on average over last 3 months >7 actuations per week and 0 or more asthma attacks	**Step up treatment (Step 2);** low dose ICS/LABA: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) one actuation twice daily **and** ICS/LABA reliever: budesonide/formoterol 200µg/6µg one actuation as required to relieve symptoms

Table 2b: Phase One AIR Algorithm Treatment Decisions Step 2

Current Treatment Step	Assessment	Treatment to be Issued
AIR Step 2: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) one actuation twice daily and one actuation as required to relieve symptoms	Reliever therapy use, on average over last 3 months ≤2 actuations per week and no asthma attack since last visit	**Step down treatment (Step 1)**; ICS/LABA reliever: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) one actuation as required to relieve symptoms
	Reliever therapy use, on average over last 3 months >2 but ≤7 actuations per week and no asthma attack since last visit	**Remain on the same step (Step 2)**; low dose ICS/LABA: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) one actuation twice daily **and** ICS/LABA reliever: budesonide/formoterol 200µg/6µg one actuation as required to relieve symptoms
	Reliever therapy use, on average over last 3 months ≤7 actuations per week and ≥1 asthma attack since last visit **or** Reliever therapy use, on average over last 3 months >7 actuations per week and 0 or more asthma attacks	**Step up treatment (Step 3);** medium dose ICS/LABA: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) two actuations twice daily **and** ICS/LABA reliever: budesonide/formoterol 200µg/6µg one actuation as required to relieve symptoms

Table 2c: Phase One AIR Algorithm Treatment Decisions Step 3

Current Treatment Step	Assessment	Treatment to be Issued
AIR Step 3: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) two actuations twice daily and one actuation as required to relieve symptoms	Reliever therapy use, on average over last 3 months ≤2 actuations per week and no asthma attack since last visit	**Step down treatment (Step 2)**; low dose ICS/LABA: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) one actuation twice daily **and** ICS/LABA reliever: budesonide/formoterol 200µg/6µg one actuation as required to relieve symptoms
	Reliever therapy use, on average over last 3 months >2 but ≤7 actuations per week and no asthma attack since last visit	**Remain on the same step (Step 3)**; medium dose ICS/LABA: budesonide/formoterol 200µg/6µg Turbuhaler (Symbicort) two actuation twice daily **and** ICS/LABA reliever: budesonide/formoterol 200µg/6µg one actuation as required to relieve symptoms
	Reliever therapy use, on average over last 3 months ≤7 actuations per week and ≥1 asthma attack since last visit **or** Reliever therapy use, on average over last 3 months >7 actuations per week and 0 or more asthma attacks	**Remain on the same step (Step 3) and on completion of the study refer to specialist for consideration of add-on therapy**

8.6.4. Educational Material

At Visit 3 all participants will have a Study Investigator explain how to use the stepwise approach to asthma management and self-adjust their own treatment steps as required. The participants that were randomised to receive the interactive educational tutorial at Visit 1 will be presented with an additional tutorial on how to use the AIR Algorithm at Visit 3.

All participants will have their understanding of the explanations provided evaluated with a second short knowledge questionnaire as per Section 8.4.3. For further detail see AIR Tutorial sub-study protocol.

8.6.5. Review of Asthma Diary Card / MyCap Mobile App

Diary cards and information from MyCap mobile app will be reviewed at each visit. The investigator will use the self-recorded data to document unplanned medical visits, details of courses of prednisone and other changes in asthma treatment.

During Phase Two participants will also be asked to report when they have “stepped up” or “stepped down” treatment level on the participant asthma diary cards or on the MyCap mobile app.

8.6.6. Medication Dispensing Post Enrolment

Participants will be issued with 0 to 5 new Symbicort Turbuhalers (depending on treatment step) at each visit. Used inhalers will be re-dispensed if they have >60 actuations left. Participants will be reminded that all dispensed inhalers (including if used or empty) are to be brought to their next study visit.

At the final visit, once the participant has completed the study, they will be issued with one new unmonitored Symbicort Turbuhaler and a prescription for two further Symbicort Turbuhalers, to ensure adequate supply until a GP appointment can be arranged.

8.6.7. Electronic Monitors and Pre-dispensing Monitor Checks

An electronic monitor will be incorporated in each turbuhaler device throughout the study. Participants will be informed that they are using a modified inhaler that has been produced specifically to count the precise number and timing of doses used during the study period. They will be informed that monitors are not to be removed, tampered with or gotten wet and that monitors will record if they have been tampered with. Monitors must be tested at each visit and prior to dispensing (see Section 10 for further details).

8.6.8. Returned Electronic Monitors

All returned electronic monitors will have a collection check performed and data will be uploaded via USB cable at each visit (for further detail see Section 10). If monitors pass the collection check then after USB upload they will be issued for re-use. Note that data uploaded from the monitors will not be discussed with the participant or used to guide treatment modification.

8.7. Participant Contact between Visits

Participants are advised to contact the investigator if:

- A healthcare provider makes any changes to their study allocated treatment.
- Following an asthma attack during Phase One (first 26 weeks).
- They are concerned they will run out of inhaler medication prior to the next study visit.
- They are concerned the allocated inhalers are not operating correctly.
- They are concerned the allocated monitors are not operating correctly.
- They wish to withdraw from the study.
- They become pregnant during the study.
- They need to re-arrange a scheduled visit.

Investigators will contact the participant prior to a scheduled visit, to confirm attendance and good health, and if:

- The participant forgets to bring their inhalers to a visit, in which case every effort should be made to have them returned to the investigator as soon as possible.
- The participant fails to attend their scheduled study appointments at the study clinics, in which case they will be contacted by telephone and arrangements made to reschedule the visit.

8.8. Unscheduled Study Visits

Unscheduled study visit refers to any visit arranged in addition to the scheduled visits and takes place outside of the scheduled visit windows.

8.8.1. Unscheduled Visit Following a Change to Study Allocated Treatment

When a healthcare provider makes a change to the study allocated treatment not in keeping with the AIR algorithm, participants will be advised to contact the investigator as soon as possible. The investigator will request attendance at an unscheduled visit as soon as practically possible. Where possible the visit will be arranged in fewer than 7 days from when the change was made.

At these visits the investigator will undertake an asthma exacerbation, adverse event and medication review (see Section 8.5 for further details). The investigator will review whether it is in the patient's interests to withdraw from the study or revert back to the study allocated treatment. Should the participant revert back to the study allocated treatment, the investigator will review whether the participant warrants treatment modification as per the AIR Algorithm (see table 2a-2c for further details).

8.8.2. Unscheduled Visit Following an Asthma Attack

Following an asthma attack during Phase One of the study (between Visit 1 and Visit 3), participants will be advised to contact the investigator as soon as possible. The investigator will request attendance at an unscheduled visit as soon as practically possible. Where possible the visit will be arranged in fewer than 7 days from the asthma attack.

At these visits the investigator will undertake an asthma exacerbation, adverse event and medication review (see Section 8.5 for further details). The investigator will review whether the participant warrants treatment modification as per the AIR Algorithm (see table 2a-2c for further details). After each asthma related hospital admission there will be central review as to whether it is in the patient's interests to withdraw from the study.

8.8.3. Unscheduled Visit for Dispensing of Trial Medication or Review of Equipment

This may occur if a participant reports they are concerned they will run out of inhaler medication prior to the next study visit or they are concerned their allocated inhalers or monitors are not operating correctly. This is to take place as soon as practically possible. Participants will be asked to bring all dispensed inhalers and monitors to the visit.

At these visits the investigator will undertake an asthma exacerbation, adverse event and medication review (see Section 8.5 for further details). Returned electronic monitors will undergo a collection check (see Section 10 for further details) and data will be uploaded via USB cable.

Participants will be issued with 0 to 5 new Symbicort Turbuhalers (depending on treatment step) with electronic monitors incorporated in each Turbuhaler device. Monitors will be tested prior to dispensing (see Section 10 for further details).

8.8.4. Unscheduled Visit for Consideration of Treatment Discontinuation/Withdrawal

Should an Investigator become aware that a participant wishes to discontinue trial treatment or withdraw from the study, or that the participant may require discontinuation from the trial treatment between study

visits, they will request attendance at an unscheduled visit. This is to take place as soon as practically possible. Participants will be asked to bring all dispensed inhalers and monitors to the visit.

At these visits the Investigator will undertake an asthma exacerbation, adverse event and medication review (see Section 8.5 for further details) and will administer the TSQM (V.II) in accordance with the TSQM user guide. Returned electronic monitors will undergo a collection check (see Section 10 for further details) and data will be uploaded via USB cable.

If the participant is withdrawn, they will be issued with 1 new unmonitored Symbicort Turbuhaler and a prescription for 2 further Symbicort Turbuhalers, to ensure adequate supply until a GP appointment can be arranged. Follow-up will continue in accordance with their scheduled study visits for the remainder of the 52-week period (see Section 8.9).

8.9. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time, without giving a reason. In addition, the Investigator may discontinue a participant from trial treatment at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation including non-compliance with treatment regimen or trial requirements
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures

Should a participant be discontinued from trial treatment, follow-up will continue in accordance with their scheduled study visits for the remainder of the 52-week period. An exception to this is if the participant declines consent to further follow up. If a participant withdraws consent for further follow-up, all data captured until the point of withdrawal of consent will be used for analysis and/ or safety reporting requirements. Participants that decline a final visit will be asked to return the study inhalers by post.

The reason for treatment discontinuation and/ or withdrawal will be recorded and the sponsor must be informed of the withdrawal as soon as is practical. If possible, participants who decide to withdraw will be asked why. If the participant discontinues trial treatment due to an adverse event, the Investigator will arrange for any necessary follow-up visits or telephone calls until the adverse event has resolved or stabilised.

8.10. Qualitative Interviews

As soon as possible after Visit 5 or after withdrawal, qualitative interviews will be conducted in person with a subset of participants using a semi-structured interview guide, to enhance understanding of the study findings. Purposive sampling will be used to provide a samples representative of participants with high and low satisfaction scores. Participants will continue to be recruited for the qualitative sub study until thematic saturation has been reached. For further detail see AIR Qualitative sub-study protocol.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1. IMP Description

Budesonide/formoterol (Symbicort) Turbuhaler 200/6µg is approved in New Zealand for the purpose of the treatment of asthma. Investigators will issue study inhalers to all participants.

9.2. IMP Labelling

IMPs will be labelled according to Good Manufacturing Practices, Annex 13, Manufacture of Investigational Medicinal Products. All IMPs will be labelled with a study label, according to local regulations and requirements. The IMP will undergo release according to Good Manufacturing Practice, with a Qualified Person providing the final sign off prior to distribution.

9.3. Electronic Monitors

Electronic monitors (Symbicort SmartTurbo, Adherium Ltd) will be incorporated in each turbuhaler device throughout the study. Pre-dispensing checks will take place at each visit (see Section 10 for further details).

9.4. Storage of IMP

All inhalers issued during the study will be stored in accordance with national guidelines. The IMPs will be stored securely, with access only given to Investigators and their delegated staff and in a suitable environment. If required, the storage of IMPs may be delegated to a pharmacy. Temperature monitored storage is required for all IMPs, from receipt at site until dispensing to participant.

9.5. Adherence with Trial Treatment

Adherence with study treatment will be captured as part of the inhaler monitor data and analysed at the end of the study. Participant self-reported inhaler use will be collected at each study Visit in order to compare with monitor data. Non-adherence will not be a cause for withdrawal and will not be reported to the participant during the study.

If a participant's asthma treatment is changed during the trial an investigator will arrange for this to revert back to the study allocated treatment as soon as possible, ideally within 7 days of the change.

9.6. Accountability of the Trial Treatment

IMPs will be dispensed at Visits 1-5 and collected at Visits 2-5. They will also be dispensed and collected at unscheduled visits as applicable. A study medication log will be provided to Investigators to record all IMPs dispensed and all IMPs collected.

Destruction of used or unused inhalers will be performed after accountability and reconciliation has taken place.

9.7. Concomitant Medication

Concomitant medications will be reviewed at screening to ensure the participant fulfils the eligibility criteria in respect to current use of asthma medications. Concomitant medications will then be recorded

during each study visit. Should a participant be prescribed additional asthma treatments, this will be documented, and the participant will remain in the study.

9.8. Post-trial Treatment

At the end of the study (Visit 5 or early withdrawal visit), participants will be issued one new budesonide/formoterol (Symbicort) Turbuhaler 200/6µg and a prescription for 2 further Symbicort Turbuhalers. Once a participant has completed the study their GP will be informed. Participants will be advised to see their GP for an asthma review within the next three months.

Participants who meet the criteria to be stepped up beyond Step 3 of the AIR Algorithm during the 12-month period will be referred for specialist review at the completion of the study.

10. ELECTRONIC MONITORING

10.1. Monitoring Kits

Participants will be allocated electronic monitors by the Investigator. Electronic monitors with unique ID numbers are to be attached to each inhaler to record the date and time of every actuation, and allow a detailed assessment of the patterns of use of the inhalers.

10.2. Monitors

Monitors will have individual ID numbers and will remain participant-specific during the course of the study. They will record the date and time of inhaler actuations. Participants will be told that they are using a modified inhaler that has been produced specifically for this study to count the precise number and timing of doses used during the study period.

Data will be uploaded via USB at each study visit via software provided by the manufacturer. Data on inhaler use will not be checked during the visit and will not be discussed with the participant.

10.3. Initial, Pre-dispensing and Collection Checks

A comprehensive trial quality control programme will be implemented for all monitors and involves testing prior to dispensing and during the full study period.

10.3.1. Initial Check

This will be completed prior to dispensing monitors for the first time. The following steps will be undertaken:

- Monitor will be woken from sleep mode by connecting the device via supplied USB cable to the manufacturer's software.
- Perform a log upload (following which the monitor clock will automatically be set to local time as set on the computer to which it is connected). Remove the monitor from the USB cord.
- Perform battery check, as per manufacturer's instruction manual. If the light does not glow green the monitor will be classed as having failed screening. Discontinue the initial check and see Section 10.3.4 for further information on failed screening.

- Attach the monitor to the inhaler, as per manufacturer's instruction manual.
- Perform two actuations, separated by 10-20 seconds, all actuation times are to be manually recorded.
- Data upload via supplied USB cable to the manufacturer's software.
- Review of data on the manufacturer's software.
- Any monitors with missing or spurious actions will be classed as having failed screening. Discrepancy between the time recorded and the data on the manufacturer's software should be less than or equal to 5 minutes.

10.3.2. Pre-dispensing Check

To be performed the day of the study visit. This does not need to be performed if an initial site check has been performed on the same day.

Battery check:

- If battery light does not flash green the monitor is deemed to have failed the check.

Actuation check:

- Two actuations performed, with the time and date recorded.
- USB upload of data to the manufacturer's software.
- Check for consistency of time and date between that recorded by investigator and that displayed on manufacturer's software.
- Any monitors with missing or spurious actions will be classed as having failed screening. Discrepancy between the time recorded and the data on the manufacturer's software should be less than or equal to 5 minutes.

10.3.3. Collection Check

To be performed the day of the study visit.

Monitor check:

- Battery check
- Any sign of damage
- If monitor passes check (displays green on battery check and has no signs of damage) then after USB upload the monitor will be issued for re-use.

10.3.4. Failed Monitors

Monitors that fail the above checks will be returned to the Sponsor for review as soon as practical. They will be replaced with another monitor, which will need to be assigned to the participant and undergo the initial site and pre-dispensing monitor checks.

10.4. Monitor Data Analysis

Data that meets dose dumping criteria will be discounted. Dose dumping is defined as greater than or equal to 100 actuations in a three-hour period.

11. SAFETY REPORTING

11.1. Definitions

Adverse Event (AE)

Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)

An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Consists of a congenital anomaly or birth defect.

Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

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

Serious Adverse Reaction (SAR)

An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:

- In the case of a product with a marketing authorisation, in the Medsafe Datasheet for that product
- In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NOTE: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".

11.2. Causality

The relationship of each adverse event to the study medication must be determined by a medically qualified individual according to the following definitions:

Related The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related The adverse event is produced by the participant's clinical state or by other modes of therapy administered to the participant.

11.3. Procedures for Recording Adverse Events

All AEs occurring during the trial that are observed by the Investigator or reported by the participant, will be recorded on the eCRF, whether or not attributed to trial medication.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

Activities of Daily Living (ADL) *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

11.3.1. Asthma Symptoms

A deterioration in asthma symptoms (wheeze, cough, chest tightness, dyspnoea, breathlessness and phlegm) will be recorded as AEs if:

- Serious Adverse Event criteria are met (see section 11.1 for definition)
- The participant is removed from treatment due to the deterioration in asthma symptoms, or
- The symptoms are new to the participant or not consistent with the participants pre-existing asthma history, as judged by the Investigator.

11.4. Reporting Procedures for Serious Adverse Events

All SAEs must be reported on the SAE reporting form to the Sponsor within 24 hours of the Study Team becoming aware of the event. The Sponsor will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Medical Monitor on a weekly basis. SAEs will also be reviewed by the Data and Safety Monitoring Committee (DSMC), in accordance with their Charter. All SAE information must be recorded on the SAE form within the eCRF, or scanned and emailed, to the Sponsor. Additional and further requested information (follow-up or corrections to the original case) may be captured within the SAE form or scanned and emailed to the Sponsor. Follow-up/ new information is required within the same reporting timeline, i.e. within 24 hours of the Study Team becoming aware of the new information.

All SAEs have to be reported, whether or not considered causally related to the investigational product. The Sponsor is responsible for informing the HDEC and/or the Regulatory Authority of the SAE as per local requirements.

11.4.1. Reporting of Serious Adverse Events to AstraZeneca

The Sponsor is responsible for informing AstraZeneca of SAEs. All SAEs will be reported to AstraZeneca, whether or not considered causally related to the investigational product.

SAEs related to the IMP must be provided to AstraZeneca within 24 hours of sponsor knowledge on an ongoing basis as individual case reports.

SAEs unrelated to the IMP must be provided to AstraZeneca as individual case reports on an ongoing basis.

At the end of the Study a final summary line listing of all SAEs notified to the regulatory authority and/or AstraZeneca during the Study, must be provided to AstraZeneca to enable reconciliation of safety information held by AstraZeneca for its product.

Send SAE reports (individual case reports and line listings) and accompanying cover page to AstraZeneca (TCS) via Email: AEmailboxclinicaltrialTCS@astrazeneca.com

SAEs that do not require expedited reporting to the Regulatory Authority/HDEC still need to be reported to AstraZeneca as individual case reports on an ongoing basis.

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to AstraZeneca at the same time these events are notified to the Regulatory Authority.

11.5. Expectedness

Expectedness will be determined according to the current version of the Medsafe Datasheet, for each applicable medicinal product respectively.

11.6. SUSAR Reporting

All SUSARs will be reported by the Sponsor to CARM (Centre for Adverse Reactions Monitoring) and to the HDEC as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

11.7. Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Sponsor.

11.7.1. Maternal exposure

If a participant becomes pregnant during the course of the study, study treatment should be discontinued and the participant should be managed by their general physician. Study follow-up will continue in accordance with Section 8.9. Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the study product may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. The outcome of all pregnancies (spontaneous miscarriage, termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented wherever possible.

If any pregnancy occurs during the course of the study, then the Investigator should inform the Sponsor no later than 24 hours of when he or she becomes aware of it.

The Sponsor will work with the Investigator to ensure that all relevant information is captured within the eCRF. If a pregnancy results in SAE criteria being met, information should be reported in accordance with SAE timelines stated above. All other pregnancy outcomes should be reported within 30 days of birth.

11.7.2. Paternal exposure

The study does not require abstinence or use of contraception for male partners of females taking part in the study. As the study medication products are not contraindicated in pregnancy, the pregnancy status of participants' partners will not be recorded.

11.8. Safety Monitoring Committee

A Data and Safety Monitoring Committee (DSMC) will be formed to conduct a review of all SAEs for the trial reported during the quarter and cumulatively. The aims of the DSMC include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

The DSMC will also undertake a review of enrolments, withdrawals, and adverse events according to the DSMC Charter, to ensure adequate study safety, and minimal risk to participants. The DSMC may recommend to the Sponsor that the study should be stopped, however the final decision will rest with the Sponsor.

12. STATISTICS

A Statistical Analysis Plan (SAP) will be developed by the Sponsor and approved by the study statistician, and finalised prior to database lock. The following information is a summary of the SAP.

12.1. Description of Statistical Methods

Categorical data will be summarised by counts and proportions expressed as percentages. Continuous data will be summarised by mean, standard deviation, median, interquartile range, and range (minimum to maximum). Full summary data for continuous variables will be reported irrespective of whether analyses based on normal distribution assumptions are used or not.

12.1.1. Primary Outcome

This trial is intended to characterise patient satisfaction with the AIR Algorithm through use of the TSQM v.II Global Satisfaction Score. TSQM Global Satisfaction Scores after 26 and 52 Weeks will be described with mean, standard deviation, median and inter-quartile range, and minimum to maximum. The 95% confidence for the mean at each measurement time, change from baseline, and for standard deviations, will be reported.

A regression approach will be used to explore if the following variables predict change from baseline TSQM Global Satisfaction Score:

- GINA 2018 treatment step at enrolment
- Age at baseline
- Sex
- Ethnicity

- Randomisation to the AIR Tutorial intervention
- History of severe exacerbation in the last 12 months
- History of moderate and severe exacerbation in the last 12 months
- Baseline FEV_1
- Baseline FeNO
- Baseline BMQ-AIR score
- Baseline BMQ-SABA score
- Baseline ACT score
- Baseline ACQ-5 score
- Baseline AQLQ-S score

12.1.2. Secondary Outcomes

Participant satisfaction with the AIR stepwise approach to the pharmacological treatment of adult asthma

- Estimate the minimal clinically important difference (MCID) for the Global Satisfaction domain of the TSQM in relation to ACQ-5, AQLQ-S, ACT, and FEV_1. The predicted mean change in TSQM from baseline in relation to each of these variables will use the MCID values for each of these variables, as detailed below in Table 4, to estimate the equivalent change.
    - Primary analysis for estimating the MCID of individual TSQM domains using a regression approach to domain scores against ACQ-5 scores.
    - Secondary analysis for estimating the MCID of individual TSQM domains will take a similar approach for AQLQ-S, ACT, and FEV_1.

Table 4: Minimal clinically important difference for ACQ-5, AQLQ-S, ACT, and FEV_1.

Instrument	Minimal clinically important difference
ACQ-5 scores	0.5 points[14]
AQLQ-S scores	0.5 points[19]
ACT scores	3 points[18]
FEV_1 measures	230 ml[20]

- Mean TSQM scores and change from baseline for each domain (effectiveness, convenience, side effects, global satisfaction) at each time point.
- Difference of mean TSQM scores for each domain from 26 Weeks will be reported at 52 Weeks.
- Participants preference scores at 26 and 52 Weeks.

Participant flow through the AIR stepwise approach to the pharmacological treatment of asthma

- Proportion of participants on each treatment step as defined by the AIR Algorithm at each timepoint.
- Proportion of participants that increase, decrease and stay on the same AIR Algorithm step, at each timepoint.
- Changes in the composition of each AIR Algorithm treatment step will be explored by flow diagrams e.g. Alluvial.
- Mean self-reported number of times AIR Algorithm treatment step was changed per participant between Week 26 and 52.
- Proportion of participants that qualified for a treatment step change Proportion of participants that qualified for a treatment step change and declined Participant led treatment step changes +/- 14 days of an asthma attack

Effectiveness of the AIR stepwise approach to the pharmacological treatment of adult asthma

- ACT score means (SD + 95% CI), change from baseline and the proportion of participants that achieved the MCID[18] will be reported at 26 and 52 Weeks.
- ACQ-5 score means (SD + 95% CI), change from baseline and the proportion of participants that achieved the MCID[14] will be reported at 26 and 52 Weeks.
- AQLQ-S score means (SD + 95% CI), change from baseline and the proportion of participants that achieved the MCID[19] will be reported at 26 and 52 Weeks.
- FEV_1 means (SD + 95% CI), change from baseline and the proportion of participants that achieved the MCID[20] will be reported at 26 and 52 Weeks.
- FeNO scores and change from baseline will be reported at 26 and 52 Weeks, likely on the logarithm transformed scale based on our previous experience with the skewed distribution of this variable and that normality assumptions were better met on the logarithm transformed scale.
- Floor and ceiling effects with respect to ACT, ACQ-5, AQLQ-S, FEV_1 and FeNO will be explored by plots to examine for non-linearity at the extremes of scores using scatter plot smoothers e.g. LOESS.
- Number and rate of severe exacerbations, and change form baseline, per patient per year at 26 and 52 Weeks.
- Number and rate of moderate and severe exacerbations, and change from baseline, per patient per year at 26 and 52 Weeks.
- Proportion of participants withdrawn and treatment discontinued and reason at 26 and 52 Weeks.

Participant beliefs about medicines used in the AIR stepwise approach to the pharmacological treatment of adult asthma

- BMQ-AIR scores (SD + 95% CI), reported as separate Necessity beliefs and Concerns scores, and change from baseline will be reported at 26 and 52 Weeks.

- BMQ-SABA scores (SD + 95% CI), reported as separate Necessity beliefs and Concerns scores, and change from baseline will be reported at 26 and 52 Weeks.

Patterns of medication use with the AIR stepwise approach to the pharmacological treatment of adult asthma

- Mean participant reported inhaler use per week over the preceding week, month and 3 months.
- Mean number of monitor recorded actuations per week over the preceding week, month and 3 months.
- Difference between mean participant reported inhaler use per week over the preceding week, month and 3 months, and mean number of monitor recorded actuations over the same time periods at 26 and 52 Weeks.
- Mean ICS dose per day at 26 and 52 Weeks.
- Mean β-agonist dose per day at 26 and 52 weeks
- Other asthma related medications taken at 26 and 52 Weeks.
- Longest duration of no actuations (days) at 26 and 52 Weeks.
- Proportion of days of no inhaler use at 26 and 52 Weeks.
- Number of days of high inhaler use (>8 actuations per 24-hour period) at 26 and 52 Weeks.
- Number of days of marked inhaler overuse (>12 actuations per 24-hour period) at 26 and 52 Weeks.
- Proportion of high inhaler use (>8 actuations per 24-hour period) episodes without medical review within 48 hours at 26 and 52 Weeks.
- Proportion of marked inhaler overuse (>12 actuations per 24-hour period) episodes without medical review within 48 hours at 26 and 52 Weeks.
- Change in inhaler use over -7 days of treatment step up and +7 days of treatment step up
- Change in inhaler use over -7 days of treatment step up and +7 days of treatment step down

Safety of the AIR stepwise approach to the pharmacological treatment of adult asthma

- Adverse events
- Proportion of participants experiencing at least 1 related adverse event at 26 and 52 Weeks.
- Serious adverse events
- Proportion of participants experiencing at least 1 related serious adverse event at 26 and 52 Weeks.

Carbon footprint as carbon dioxide-equivalent (CO2e) emissions per person year

- A carbon footprint analysis will be undertaken that calculates the net asthma carbon footprint per participant, expressed as carbon dioxide equivalents (CO_2e). This will include inhaler devices and healthcare encounters for asthma exacerbations, calculated using previously published and publicly available data. Imputation will not be used for missing data; instead, the emission will be

adjusted for participant time on the trial medication, so it corresponds to 26 and 52 weeks on treatment.

For further details on the AIR Tutorial and AIR Qualitative sub-study outcome measures see separate sub-study protocols.

12.2. The Number of Participants

The study will recruit 25 participants from each of the first four GINA 2018 treatment steps, 100 participants in total. The sample size of 25 participants is chosen to give reasonable precision (based on about 20 degrees of freedom) for estimation of standard deviations within each block.

12.3. The Level of Statistical Significance

Although a nominal level of significance is P ≤0.05, expressed as 95% confidence intervals, will be used, there will be no adjustment of significance levels for multiple statistical testing and inflation of Type I error.

12.4. Criteria for the Termination of the Trial

The trial may be terminated early for safety reasons, for example if the Sponsor believes there is a safety risk to participants, or if the HDEC terminates or suspends its approval/favourable opinion of the trial.
If the trial is terminated early or suspended, the Sponsor should promptly inform the HDEC (either of its decision, or to confirm the trial has been terminated in accordance with HDEC requirements) and provide a detailed written explanation for the termination or suspension. The study site will be informed within 1 working day of the decision to terminate or suspend the trial.

12.5. Procedure for Accounting for Missing, Unused, and Spurious Data

For the primary outcome, data imputation will not be used for those who withdraw from the study before the planned completion date (e.g. due to withdrawal of consent or loss to follow-up) because it cannot be assumed that their subsequent data will be completely missing at random.

For repeated measured analyses of continuous variables, mixed linear models will be used which assume missing data are missing at random.

12.6. Inclusion in Analysis

For calibration of the TSQM Global Satisfaction MCID, the analysis dataset will include all participants enrolled up until the point of withdrawal, unless potential participants were actually ineligible, and so enrolled in error.

The analysis dataset for all other outcomes will include all participants enrolled, up until the point of discontinuation of study treatment or withdrawal, unless as described above, potential participants were actually ineligible, and so enrolled in error. For participants that have discontinued from study treatment, post discontinuation characteristics will be described.

No data collection is planned relating to dates after withdrawal of consent for continued data collection. Data imputation will not be used for those who withdraw consent for continued data collection before the planned Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan will be described and justified in the final report.

13. DATA MANAGEMENT

13.1. Source Data

Source data refers to where data are first recorded, and from which participants' study data are obtained. Source documents include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, radiographs, correspondence and audio recordings. Study data are collected into a Clinical Data Management Application (CDMA) in which entries will be considered source data if the CDMA is the site of the original recording (e.g. there is no other written or electronic record of data).

13.2. Access to Data

Direct access to source and study data will be granted to authorised representatives from the Sponsor, and the regulatory/ ethics authorities to permit trial-related monitoring, audits and inspections.

13.3. Data Recording and Record Keeping

Data will be entered into the REDCap electronic data capture tool hosted and supported by the MRINZ. REDCap is a secure, HIPAA (United States Health Insurance Portability and Accountability Act 1996) compliant web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages, including de-identified data sets; and 4) procedures for importing data from external sources.

The AIR Qualitative sub-study will involve interviews conducted in English, audio recorded, and then transcribed verbatim. The data will be uploaded to NVivo for data management and coding. NVivo is a qualitative data analysis computer software package.

Participants will be identified by a unique study ID in any data export from the eCRF database. The name and any other identifying detail will not be included within the eCRF.

The MyCap mobile extension of REDCap installed on participants' mobile devices will allow direct, secure self-reported data entry and syncs directly with their research record. Participants will be able to log unplanned medical visits, details of courses of prednisone and other changes in asthma medications/ treatment.

Source and Essential documents will be stored at Site for a minimum of 15 years after the completion of the trial, in accordance with GCP. Study Data held within the eCRF and Essential Documents held in the Trial Master File (TMF) will be stored by the Sponsor for a minimum of 15 years after the completion of the trial, in accordance GCP.

14. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to GCP, as defined within the study Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures/ the Monitoring Plan, the Monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Data will also be monitored by the DSMC in accordance with Section 11.8. and the DSMC Charter.

The Trial Management Group (TMG) will meet regularly to discuss the progress of the trial and for the purpose of assuring quality, in their role of executing the function of Sponsor. The Trial Management Group will be formed of Sponsor staff with relevant expertise in conducting multi-centre trials.

The Trial Steering Committee (TSC) will meet formally every 6 months, in accordance with the TSC Charter, to discuss the progress of the trial, including DSMC correspondence and the outcome of site monitoring visits if appropriate.

15. SERIOUS BREACHES

The HDEC SOPs (August 2014) define a protocol violation as a "deviation that may affect participants' rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Deviations/violations may occur without the knowledge or permission of the sponsor or the CI, and may constitute fraud or misconduct." Violations are events that are likely to affect to a significant degree any of the following:

- the safety or physical or mental integrity of participants
- the scientific value of the study
- the conduct or management of the study
- the quality or safety of any medicine or item used in the study

In the event that a protocol violation is suspected the Sponsor must be contacted within 1 working day. In collaboration with the Investigator the violation will be reviewed by the Sponsor and, if deemed appropriate, it will be reported to the responsible HDEC, regulatory authority, and local governance body (as applicable) within seven working days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

The study does not require submission to Medsafe (via the Standing Committee on Therapeutic Trials) under Section 30 of the Medicines Act 1981, as the study IMP is an approved product in New Zealand, for the purpose of the treatment of asthma.

Ethical Submission will be made to one of the Health and Disability Ethics Committees of New Zealand. The opinion/ approval of the Ethics Committee will be given in writing. Locality approval must be granted before any participants are recruited, as per Ethics Committee guidelines. The Ethics Committee should approve all advertising used to recruit patients for the study.

Approval for the study will also be sought from an appropriate Māori Consultation body, and such approval will be given prior to Locality approval being issued.

The Chief/ Co-ordinating Investigator will submit all substantial amendments to the original approved documents to the HDEC for review and approval. The Sponsor should approve any modifications to any documents provided to the HDEC.

16.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the HDEC and Sponsor. In addition, a Notification of Completion form and final report will be submitted to the HDEC and Sponsor, in accordance with their requirements.

16.5. Participant Confidentiality

Data will be collected, used and stored in accordance with applicable Site and Sponsor SOPs and the Health Information Privacy Code 1994, the Code of Health and Disability Services Consumers Rights 1996, and the Bill of Rights Act 1990.

The study staff will ensure that the participant's privacy is maintained. Participant identifiable data will be captured as part of source data, which will only be accessible to authorised Site staff members.

Participant identifiable information including name, contact details, NHI number, date of birth and ethnicity will be collected in the Clinical Data Management Application (CDMA) which is designed to collect all the study information at a site. The CDMA is accessible only to site staff; sponsor staff cannot access the CDMA unless with specific permission, thereby maintaining participant confidentiality.

Protocol-defined data will be extracted from the CDMA into a separate application termed the eCRF, which can be accessed by sponsor staff. Limited personal information (e.g. date of birth and demographic details) will be pulled into the eCRF as they will be required as part of the study analysis. Name and contact details will not be pulled into the eCRF; participants will be identified by a unique participant number. The CDMA and eCRF are encrypted, secure systems, protected by unique username and password requirements for log-in, which are only provided to trained study staff.

Individual patient GP address is being captured centrally by the Medical Research of New Zealand (study Sponsor) so that participants' GPs can be informed of their involvement in the trial.

The NHI number will be collected to assess the agreement between participant reported details and electronic health records of exacerbations. This will be outlined specifically to the participants in the PIS-CF so that they are aware of this provision of their data and can provide their consent to its use in this way. The Sponsor will only use a participant's NHI number and other personal information for the purposes outlined above. No study reports will contain any information that could individually identify a study participant.

Data recorded in the CDMA and CRF (including MyCap) will be securely stored on servers in New Zealand and Australia.

De-identified data recorded by the electronic monitors will be securely stored on servers in New Zealand and Australia.

Anonymised data from the TSQM will be exported to IQVIA (a global company and proprietor of the TSQM) for the sole purpose of improving the psychometric properties of the licenced materials. Where these, and other questionnaires are signed by study participants, the questionnaire data will be pulled into the eCRF, identified by unique study identifier, but no names or signatures will be stored in the eCRF.

The Sponsor (via the Study Monitor) will have access to the identifiable source data at site, for on-site monitoring purposes, to ensure the study is being run in compliance with GCP and the protocol.

16.6. Expenses and Benefits

Participants will be eligible for reasonable reimbursement for their time and travel costs in attending study visits. The reimbursement amount will be included in the PIS-CF and must be approved by the responsible HDEC.

16.7. Other Ethical Considerations

All participants enrolled in the study will receive regular follow-up and will be allocated an appropriate intervention based on their pre-enrolment GINA treatment step.

17. FINANCE AND INSURANCE

17.1. Funding

This study will be supported by the HRC Independent Research Organization Funding. Study medication, electronic monitors and funding to support electronic monitor data collection will be supplied by AstraZeneca, a global research-based biopharmaceutical company.

17.2. Insurance

This study is not being conducted for the benefit of a drug manufacturer or distributor and therefore clinical trial insurance to cover participant injury due to participation in the study is not required. Participants may claim under the Accident Compensation Act 2001 for injury sustained during the study, if appropriate.

18. PUBLICATION POLICY

The study findings will be published by the Sponsor, in a scientific peer reviewed journal, according to the International Committee of Medical Journal Editors recommendations. The Investigators listed on page one will be listed as authors, in recognition of their contribution to the design, implementation and oversight of the study.

Results of the study will be sent to participants on request (once available) and will be made available on a publicly available trial registry website, recognised by the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) as a Primary Registry.

19. REFERENCES

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APPENDIX A: TRIAL REGIMEN, GINA 2018 REGIMEN AND TRIAL FLOW DIAGRAM

Figure 1: The Symbicort Anti-inflammatory Reliever Therapy Algorithm

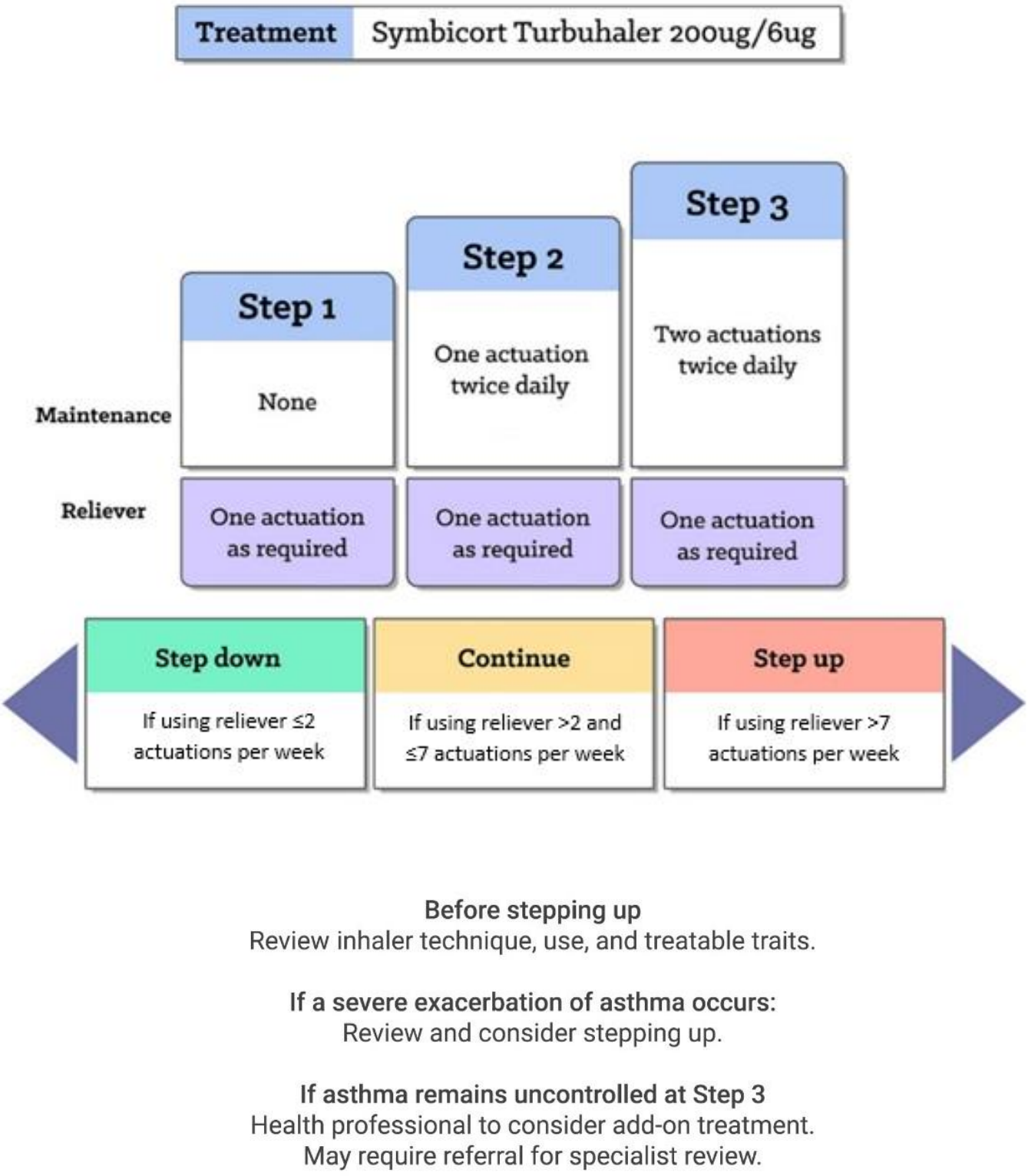


Figure 2: The Traditional GINA 2018 Algorithm

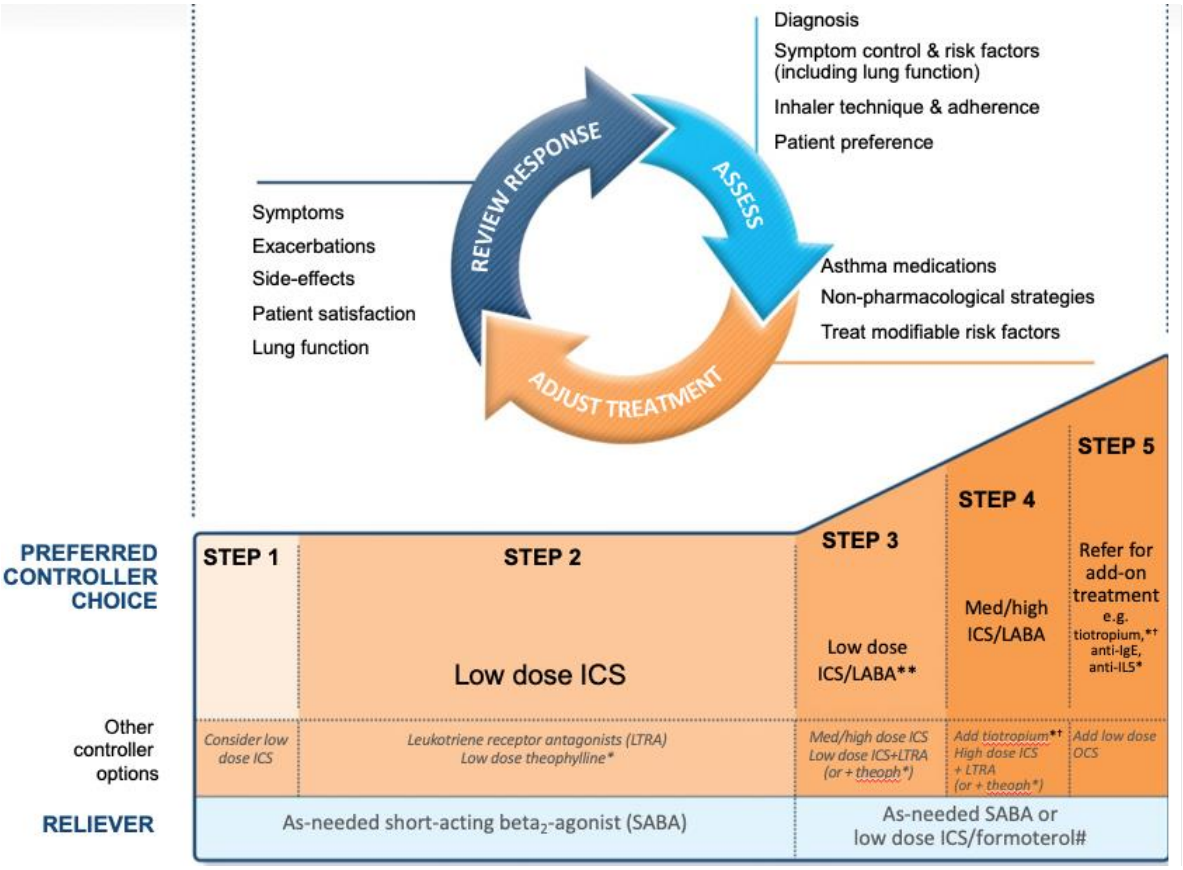
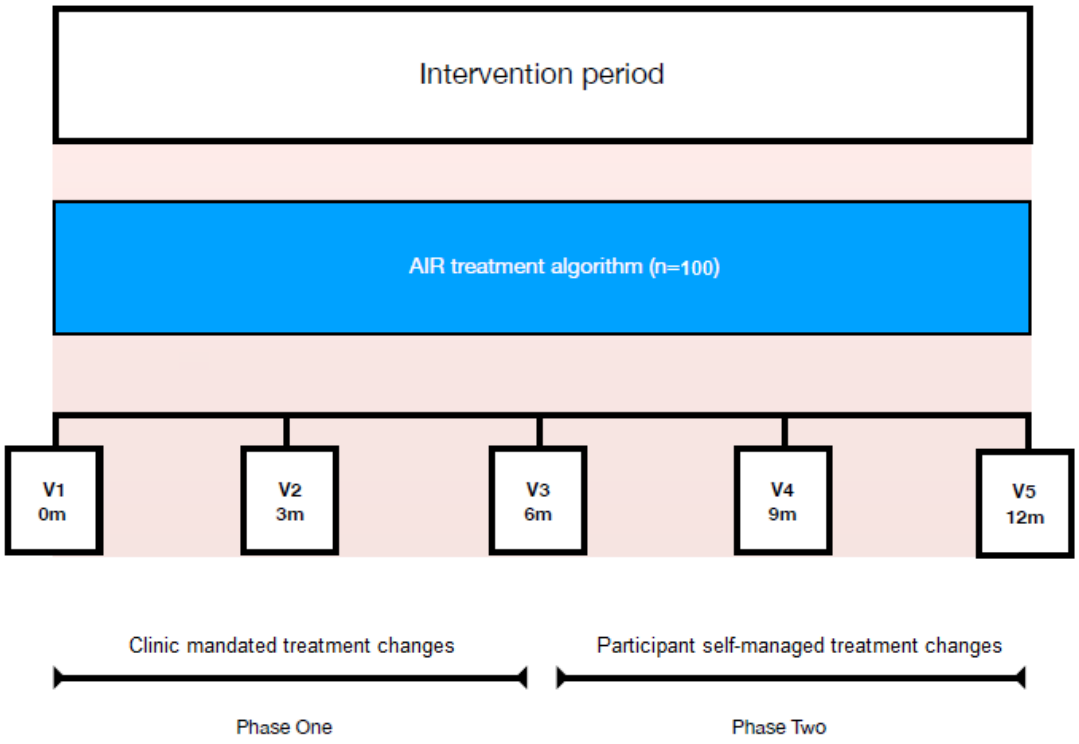


Figure 3: Low, Medium and High Daily Dose of Inhaled Corticosteroids

Drug	**Daily dose (mcg)**		
	Low	**Medium**	**High**
Budesonide e.g. Pulmicort, Symbicort, Vannair	200-400	>400-800	>800
Fluticasone propionate e.g. Flixotide, Seretide, Floair, RexAir	100-250	>250-500	>500
Fluticasone Furoate e.g. Breo Ellipta	N/A	100	200
Beclomethasone Dipropionate Standard particle e.g. Beclazone	200-500	>500-1000	>1000
Extrafine particle e.g. QVAR	100-200	>200-400	>400

Figure 4: Trial Flow Diagram



APPENDIX B: SCHEDULE OF PROCEDURES

Visit Number	Consent & Enrolment	1	2	3	4	5	±6	Unscheduled Visits
Week	≤1	1	13	26	39	52	A/R	A/R
Day	≤1	1	91	182	273	364	A/R	A/R
Visit Window (Days)	N/A	N/A	±7	±7	±7	±7	N/A	N/A
Written informed consent (including e-signature)	X							
Demographics, Height and Weight	X	X*						
Medical history (including asthma history and concomitant medication)	X	X*						
Pregnancy status	X	X*	X	X	X	X		
Smoking cessation advice	X	X*						
Inclusion / Exclusion criteria check	X	X*						
TSQM v.II Questionnaire		X	X	X	X	X		A/R
ACQ-5 Questionnaire		X		X		X		
AQLQ-S Questionnaire		X		X		X		
ACT Questionnaire		X		X		X		
BMQ-SABA Questionnaire		X		X		X		
BMQ-AIR Questionnaire		X		X		X		
Participant Management Preference Question				X		X		
FeNO†		X		X		X		
Spirometry		X		X		X		
Assess Symbicort use			X	X	X	X		A/R
Review: • Asthma exacerbations • AEs / SAEs‡ • Medication changes			X	X	X	X		X
Review self-adjusted treatment step changes					X	X		
Allocation of treatment according to algorithm		X	X	X		X		A/R
Issue/review written asthma action plan		X	X	X	X	X		A/R
Review inhaler technique		X	X	X	X	X		A/R
Investigator led explanation of study material		X		X				
Participants randomised to AIR Tutorial		X						
AIR Tutorial materials presented		X	X	X	X	X		
Upload data from electronic monitors via USB cable			X	X	X	X		A/R
Electronic monitor checks		X	X	X	X	X		A/R
Issue study inhalers with electronic monitors attached		X	X	X	X			A/R
Issue post study inhaler and prescription						X		A/R
Qualitative Interview#							X	
Inform GP of study enrolment		X						
Inform GP of study completion / withdrawal			A/R	A/R	A/R	X		A/R

*Reviewed if consent and enrolment done on a different day to Visit 1; †Performed prior to spirometry; ‡Investigator to inform Sponsor within 24 hours of becoming aware of an SAE (for further detail see Protocol Section 11); #Subset of participants that have consented for interview (AIR-Q) following last trial visit; A/R = As Required; N/A = Not Applicable

APPENDIX C: PARTICIPANT REPORTED OUTCOME QUESTIONNAIRES

Figure 5: Treatment Satisfaction Questionnaire for Medication (TSQM v.II)

TSQM *(Version II)* Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please select a single response that most closely corresponds to your own experiences.

---

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐ 1 Yes
☐ 0 No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g. strength, energy levels)?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Somewhat Dissatisfied
☐ 4 Slightly Dissatisfied
☐ 5 Not at all Dissatisfied
☐ (5) Not Applicable

5. How dissatisfied are you by side effects that interfere with your mental function (e.g. ability to think clearly, stay awake)?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Somewhat Dissatisfied
☐ 4 Slightly Dissatisfied
☐ 5 Not at all Dissatisfied
☐ (5) Not Applicable

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g. anxiety/fear, sadness, irritation/anger)?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Somewhat Dissatisfied
☐ 4 Slightly Dissatisfied
☐ 5 Not at all Dissatisfied
☐ (5) Not Applicable

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐ 1 Extremely Dissatisfied
☐ 2 Very Dissatisfied
☐ 3 Dissatisfied
☐ 4 Somewhat Satisfied
☐ 5 Satisfied
☐ 6 Very Satisfied
☐ 7 Extremely Satisfied

Figure 6: Beliefs about Medicines Questionnaire – Anti-Inflammatory Reliever (BMQ-AIR)

YOUR VIEWS ABOUT
Your Anti-Inflammatory Reliever (AIR) Inhaler

- We would like to ask you about your personal views about the AIR Inhaler prescribed for you
- These are statements other people have made about their AIR Inhaler.
- Please show how much you agree or disagree with them by ticking the appropriate box.

There are no right and wrong answers.
We are interested in your personal views

	Views about YOUR ANTI-INFLAMMATORY RELIEVER INHALER (AIR)	***Strongly Agree***	***Agree***	***Uncertain***	***Disagree***	***Strongly Disagree***
N1	*Replacing my old reliever with this AIR inhaler will work/ works well for me*					
C1	*Having to use this AIR inhaler worries me*					
N2	*Using this AIR inhaler will be/is a better way of managing my asthma than using a preventer and reliever separately*					
N3	*This AIR inhaler will be/is the most important part of my asthma treatment*					
C2	*I worry about the long-term effects of this AIR inhaler*					
C3	*I don't like the idea of using a steroid inhaler more often*					
N4R	*Combining a preventer and reliever in one inhaler WILL/ DOES NOT suit me*					
C4	*This AIR inhaler will cause/causes unpleasant side effects*					
C5	*I am concerned about becoming too dependent on this AIR inhaler*					
N5	*This AIR inhaler will be/is effective in managing my asthma symptoms*					
C6R	*I have been given enough information about this AIR inhaler*					
N6	*This AIR inhaler will help prevent future asthma attacks.*					
N7	*If I were having an asthma attack I wouldn't worry about not having my old reliever inhaler, as long as I had this AIR inhaler with me*					
C7	*I am concerned that this AIR inhaler might be LESS safe than my old reliever*					
C8	*I am concerned that this AIR inhaler might become less effective if I use it regularly*					

Figure 7: Beliefs about Medicines Questionnaire – Short Acting Beta Agonist (BMQ-SABA)

YOUR VIEWS ABOUT THE
YOUR BLUE RELIEVER INHALER

- We would like to ask you about your personal views about **YOUR BLUE RELIEVER INHALER**
- These are statements other people have made about their **BLUE RELIEVER INHALER**.
- Please show how much you agree or disagree with them by ticking the appropriate box.

There are no right or wrong answers.
We are interested in your personal views

	Views about YOUR BLUE RELIEVER INHALER	***Strongly Agree***	***Agree***	***Uncertain***	***Disagree***	***Strongly Disagree***
N1	Using my RELIEVER inhaler to treat symptoms is/was the best way to keep on top of my asthma					
C1	Having to use my RELIEVER inhaler worries/worried me					
N2	I don't/didn't worry about asthma when I have/had my RELIEVER inhaler around					
C2	I worry/worried about the long-term effects of my RELIEVER inhaler					
N3	My RELIEVER inhaler is/was the only asthma treatment I can/could really rely on					
C3	My RELIEVER inhaler causes/caused unpleasant side effects					
N4	The benefits of using my RELIEVER inhaler easily outweigh/ outweighed any risks					
C4	I am/was concerned about becoming too dependent on my RELIEVER inhaler					
N5	I prefer/preferred to rely on my RELIEVER inhaler than my STEROID PREVENTER inhaler					
C5R	I have been given enough information about my RELIEVER inhaler					
C6	I am/was concerned that my RELIEVER inhaler might become less effective if I use/used it regularly					

Figure 8: Asthma Control Test (ACT)

Asthma Control Test™

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an ☒ in the one box that best describes your answer.

1. In the <u>past 4 weeks</u>, how much of the time did your <u>asthma</u> keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

2. During the <u>past 4 weeks</u>, how often have you had shortness of breath?

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐1	☐2	☐3	☐4	☐5

3. During the <u>past 4 weeks</u>, how often did your <u>asthma</u> symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐1	☐2	☐3	☐4	☐5

4. During the <u>past 4 weeks,</u> how often have you used your blue puffer or reliever medication (such as Ventolin®, Respigen®, SalAir®, Asthalin® or Bricanyl®)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
☐1	☐2	☐3	☐4	☐5

5. How would you rate your <u>asthma</u> control during the <u>past 4 weeks</u>?

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐1	☐2	☐3	☐4	☐5

Figure 9: Asthma Control Questionnaire (ACQ-5)

ASTHMA CONTROL QUESTIONNAIRE©

Please answer questions 1 - 5.

Circle the number of the response that best describes how you have been in the last week.

1.	In general, during the **past week**, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	In general, during the **past week**, how **uncomfortable were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the **past week**, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the **past week**, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5.	In general, during the **past week**, how much time did you **wheeze?**	0 Never 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time

Figure 10: Asthma Quality of Life with Standardised activities Questionnaire (AQLQ-S)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) ©

Please complete **all** the questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK/SCHOOL-RELATED ACTIVITIES* (tasks you have to do at work/in school)	1	2	3	4	5	6	7
5. SLEEPING	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7

8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTER SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a	1	2	3	4	5	6	7

result of your asthma?							
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION/POLLEN OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION/POLLEN?	1	2	3	4	5	6	7
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have the feeling of FIGHTING FOR BREATH?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS?**

	Severely Limited Most Activities Not Done	Very Limited	Moderately Limited Several Activities Not Done	Slightly Limited	Very Slightly Limited Very Few Activities Not Done	Hardly Limited At All	Not Limited At All Have Done All Activities That I Wanted To Do
31. Think of all the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

Figure 11: Participant Management Preference Question

"How did you find your study treatment relative to your previous treatment?"

Participant to complete on 5-point Likert scale (e.g. 1. Much worse 2. Somewhat worse 3. The same 4. Somewhat better 5. Much better)

APPENDIX D: ASTHMA DIARY AND ACTION PLAN / MYCAP MOBILE APP

Figure 12: Phase One Asthma Diary and Action Plans (clinic mandated treatment changes)

Page 1

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

AIR ALGORITHM STUDY

ASTHMA DIARY & ACTION PLAN

Name .....

Date of plan .....

GP .....

GP phone .....

Page 2

Using your Symbicort Turbuhaler

1. Unscrew and remove the protective cover
2. Hold the Turbuhaler upright
3. Twist the coloured grip as far as it will go in one direction and then back again until you hear a click
   - Your Turbuhaler is now loaded with a dose of medication
4. Breathe out gently, away from mouthpiece
5. Place the mouthpiece between your lips:
   - Suck in deeply and forcefully through the Turbuhaler. You may not taste or feel the medication
   - Remove the inhaler from your mouth and breathe out. Do not breathe back into the mouthpiece as you will make it damp inside
   - If more than one actuation is required, repeat the steps above
   - When you are finished, place the cover back on the inhaler and twist shut
6. Your Turbuhaler has an actuation indicator window just below the mouthpiece, when you see red in the window it is time to get a new Turbuhaler

Caring for your Turbuhaler

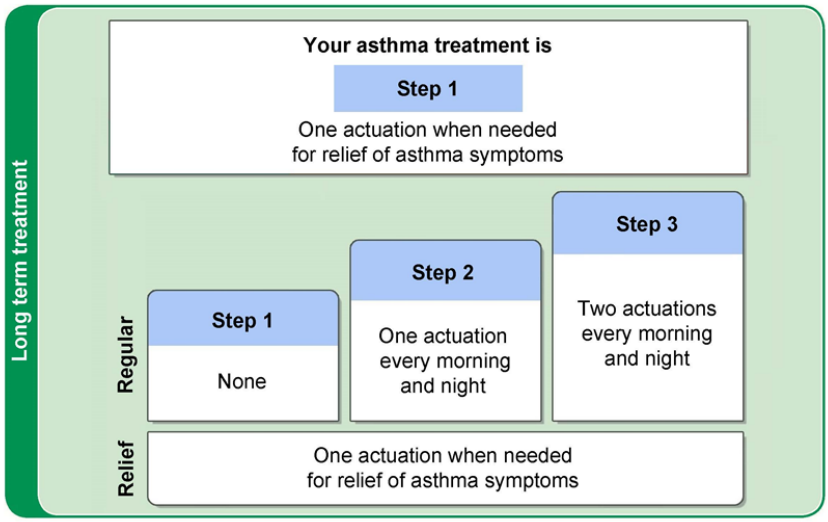
1. Do not wash your Turbuhaler as it will not work properly if it gets wet
2. Wipe the mouthpiece with a dry tissue or cloth

Page 3.1 - AIR Algorithm Treatment Step 1

AIR adult asthma

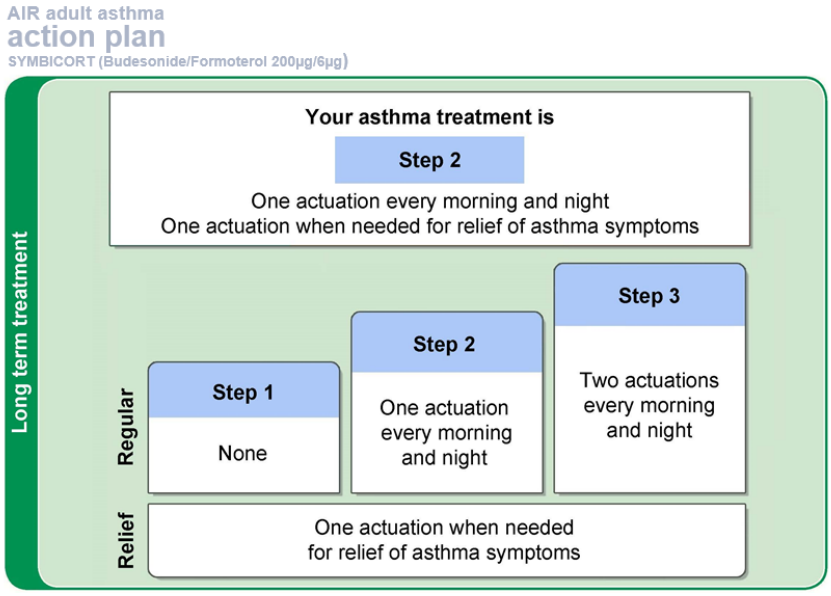
action plan

SYMBICORT (Budesonide/Formoterol 200µg/6µg)

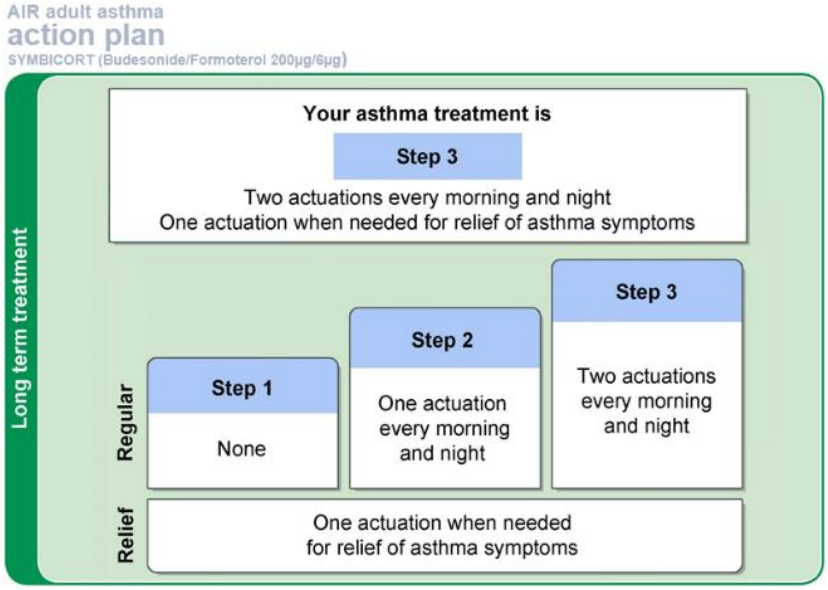


NOTE: Participants will be provided with an action plan specific to their allocated treatment step. If their treatment step is changed they will be provided with a new action plan specific to their newly allocated treatment step.

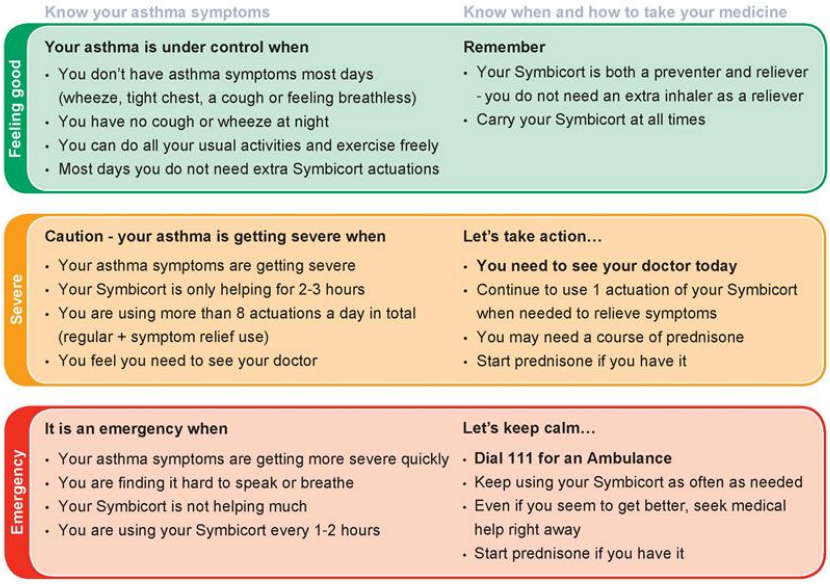
Page 3.2 - AIR Algorithm Treatment Step 2



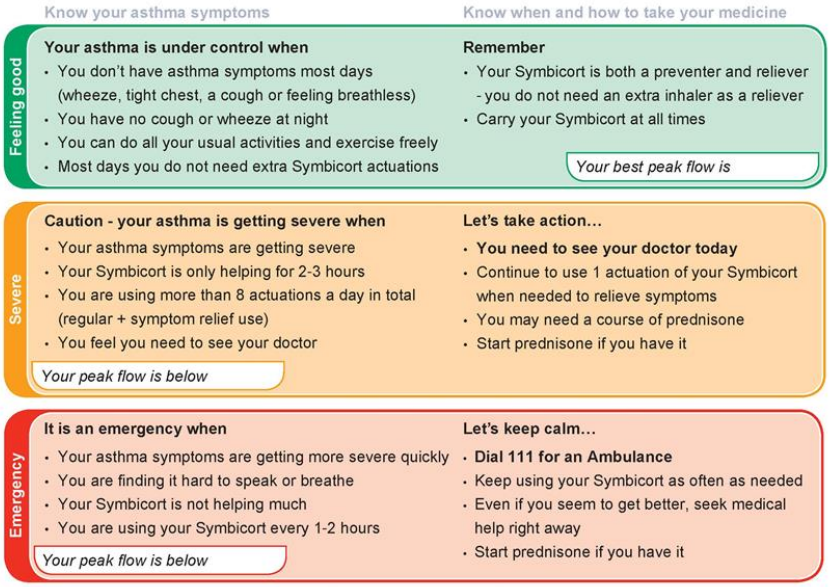
Page 3.3 - AIR Algorithm Treatment Step 3



Page 4.1



Page 4.2 - incorporating peak flow use



NOTE: An action plan incorporating peak flow use will only be provided to participants who already monitor their peak flows on entry to the study. Best peak flow will be documented at baseline by participant self report. Severe: a drop in peak flow to <60% of recent best. Emergency: a drop in peak flow to <40% of recent best.

Page 5

Asthma Attacks

An Asthma Attack is any time you need prednisone tablets because your asthma symptoms have become worse. If you have had a recent Asthma Attack, please contact the Study Investigator to arrange a review of your study treatment.

Asthma Diary

If you are noting this information on MyCap mobile app you do not need to copy it here.

If you have needed urgent medical help from your GP, After Hours or Emergency Department, been admitted to Hospital or taken prednisone due to asthma, please fill details below.

Date	Services used? *e.g. GP*	Prednisone taken? *(Yes/No)*	Prednisone dose *e.g. 40mg*	How long for? *e.g. 4 days*	Date started	Date stopped	Comments *e.g. Admitted*

Page 6

New Medications

If you have had any recent changes to your asthma medication, please contact the Study Investigator to arrange a review of your study treatment.

If you have started any new medication or if you have had any changes to existing medications, please fill details below.

Medication started/ changed *e.g. Amoxicillin*	Dose *e.g. 500mg*	How many times a day? *e.g. Once a day*	How long for? *e.g. 5 days*	Date started/ changed	Date stopped	Comments/Reason for medication *e.g. Sore throat*

Page 7

Investigator Contact Details

Name .....

E-Mail .....

Phone number .....

The Investigator will be available to take your call/email during business hours, Monday to Friday.

Please contact the Investigator if:

- You are concerned you will run out of inhaler medication before your next study visit
- You are concerned your inhalers are not working properly
- You wish to withdraw from the study
- You become pregnant
- You have had a recent asthma attack
- Your asthma treatment has been changed

If you need medical help for your asthma, please contact your GP, After Hours Service or an Ambulance as appropriate. This is important, to make sure you get treated quickly in accordance with standard practice.

Study Appointment Dates & Times	Treatment Step
Visit 1	.....
Visit 2	.....
Visit 3	.....

Additional Notes

.....

.....

.....

Figure 13: Phase Two Asthma Diary and Action Plans (self-managed treatment changes)

Page 1

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

AIR ALGORITHM STUDY

ASTHMA DIARY & ACTION PLAN

Name .....

Date of plan .....

GP .....

GP phone .....

Page 2

Using your Symbicort Turbuhaler

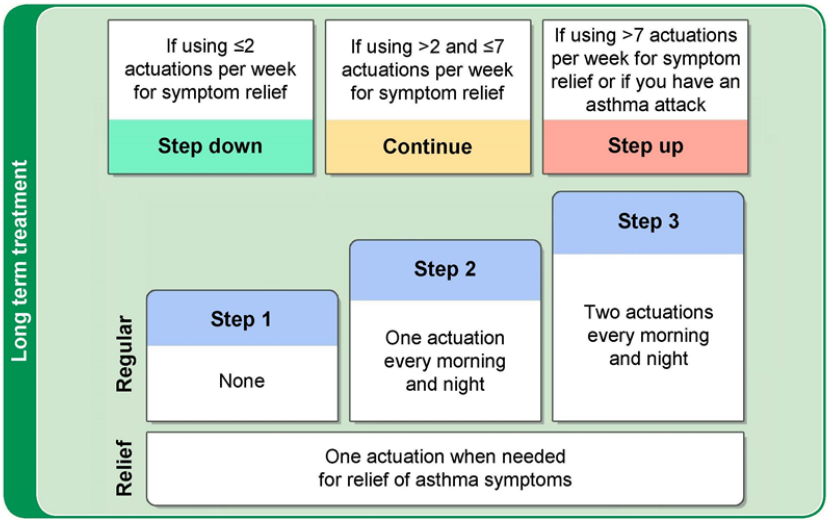
1. Unscrew and remove the protective cover
2. Hold the Turbuhaler upright
3. Twist the coloured grip as far as it will go in one direction and then back again until you hear a click
   - Your Turbuhaler is now loaded with a dose of medication
4. Breathe out gently, away from mouthpiece
5. Place the mouthpiece between your lips:
   - Suck in deeply and forcefully through the Turbuhaler. You may not taste or feel the medication
   - Remove the inhaler from your mouth and breathe out. Do not breathe back into the mouthpiece as you will make it damp inside
   - If more than one actuation is required, repeat the steps above
   - When you are finished, place the cover back on the inhaler and twist shut
6. Your Turbuhaler has an actuation indicator window just below the mouthpiece, when you see red in the window it is time to get a new Turbuhaler

Caring for your Turbuhaler

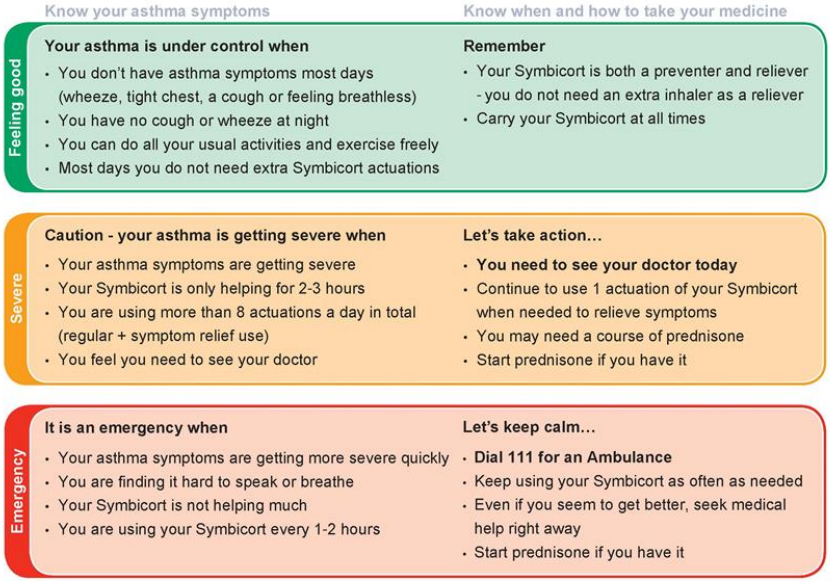
1. Do not wash your Turbuhaler as it will not work properly if it gets wet
2. Wipe the mouthpiece with a dry tissue or cloth

Page 3

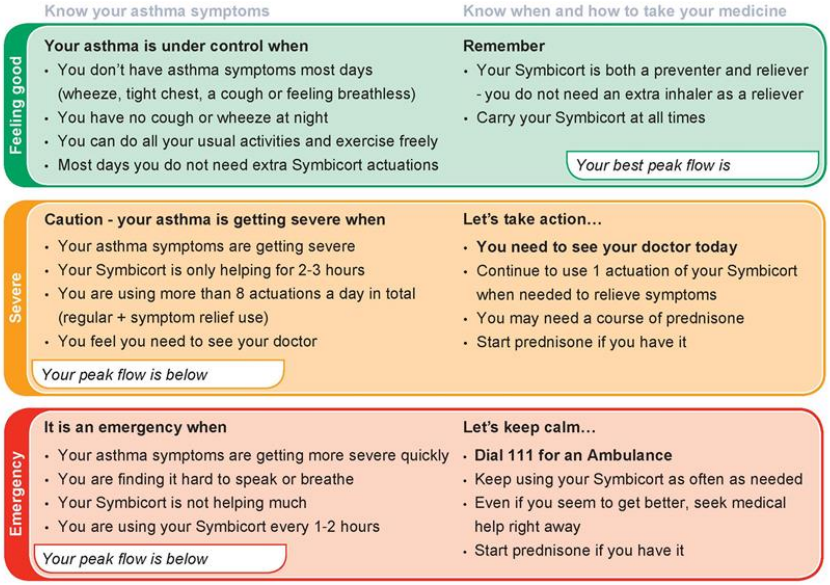
AIR adult asthma
action plan
SYMBICORT (Budesonide/Formoterol 200µg/6µg)



Page 4.1



Page 4.2 - incorporating peak flow use



NOTE: An action plan incorporating peak flow use will only be provided to participants who already monitor their peak flows on entry to the study. Best peak flow will be documented at baseline by participant self report. Severe: a drop in peak flow to <60% of recent best. Emergency: a drop in peak flow to <40% of recent best.

Page 5

Asthma Attacks

An Asthma Attack is any time you need prednisone tablets because your asthma symptoms have become worse.

Asthma Diary

If you are noting this information on MyCap mobile app you do not need to copy it here.

If you have needed urgent medical help from your GP, After Hours or Emergency Department, been admitted to hospital or taken prednisone due to asthma, please fill details below.

Date	Services used? *e.g. GP*	Prednisone taken? *(Yes/No)*	Prednisone dose *e.g. 40mg*	How long for? *e.g. 4 days*	Date started	Date stopped	Comments *e.g. Admitted*

Page 6

New Medications

If you have had any recent changes to your asthma medication, please contact the Study Investigator to arrange a review of your study treatment.

If you have started any new medication or if you have had any changes to existing medications, please fill details below.

Medication started/ changed *e.g. Amoxicillin*	Dose *e.g. 500mg*	How many times a day? *e.g. Once a day*	How long for? *e.g. 5 days*	Date started/ changed	Date stopped	Comments/Reason for medication *e.g. Sore throat*

Page 7

Treatment Step Changes

If you have “stepped up” or “stepped down” your asthma treatment please fill details below.

Date	Step change? *(Up/Down)*	What Step are you on now? *e.g. Step 2*

Page 8

Investigator Contact Details

Name .....

E-Mail .....

Phone number .....

The Investigator will be available to take your call/email during business hours, Monday to Friday.

Please contact the Investigator if:

- You are concerned you will run out of inhaler medication before your next study visit
- You are concerned your inhalers are not working properly
- You wish to withdraw from the study
- You become pregnant
- Your asthma treatment has been changed

If you need medical help for your asthma, please contact your GP, After Hours Service or an Ambulance as appropriate. This is important, to make sure you get treated quickly in accordance with standard practice.

Study Appointment Dates & Times	Treatment Step
Visit 3	.....
Visit 4	.....
Visit 5	.....

Additional Notes

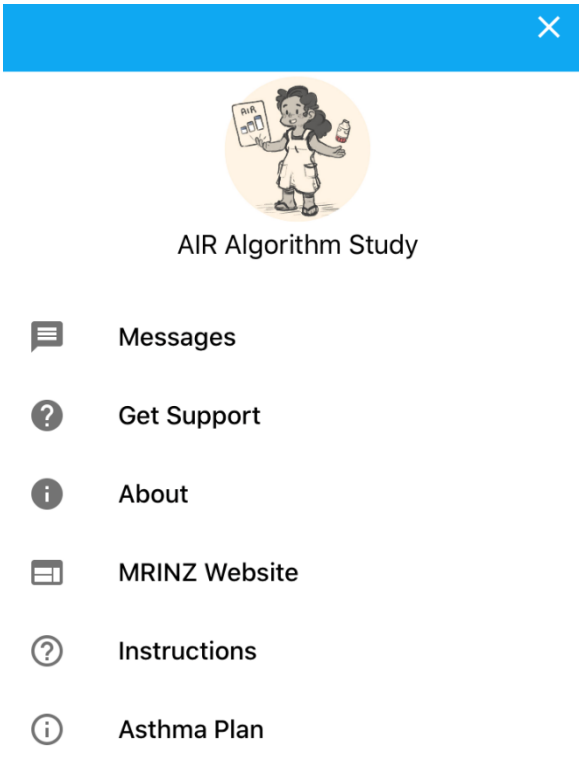
.....

.....

Figure 14: MyCap Mobile App

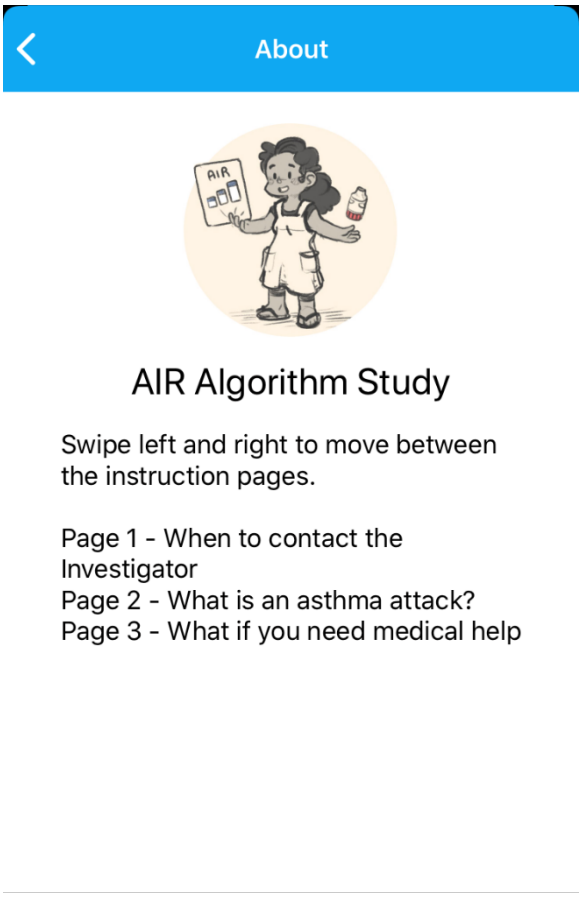
Phase One MyCap Screenshots

1.1 Menu



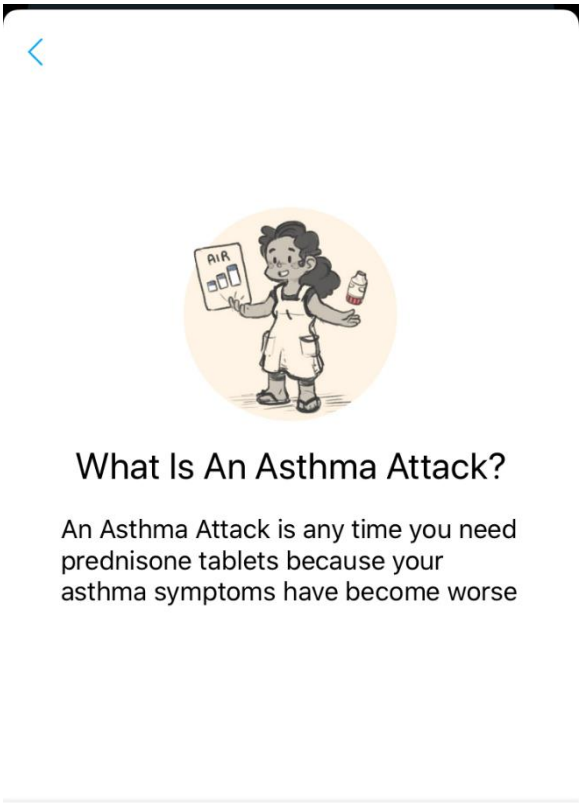
1.1.1 Get Support

1.1.2 About Summary

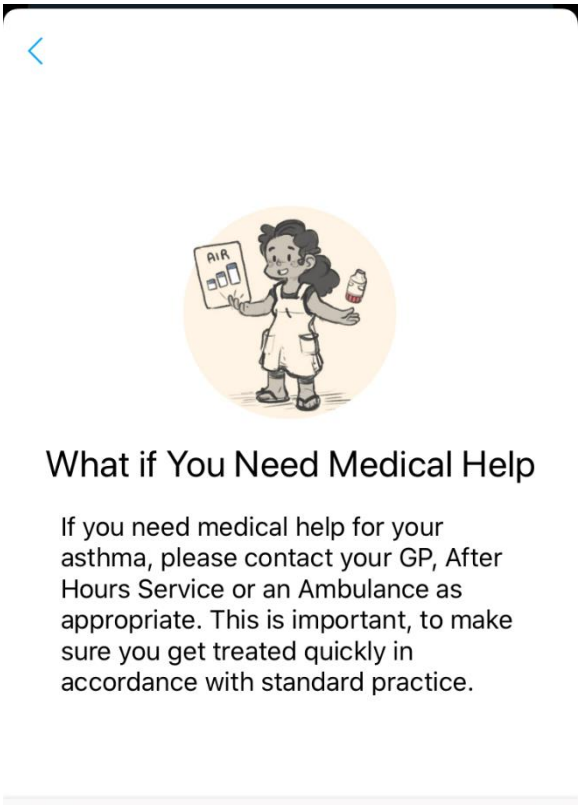


1.1.2.1 When to contact the Investigator

1.1.2.2 What is an asthma attack?

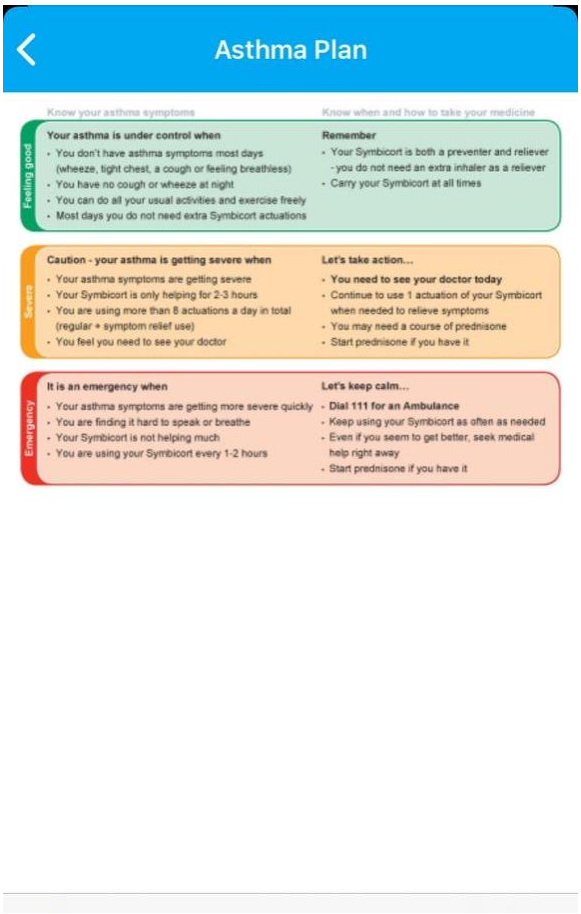


1.1.2.3 What if you need medical help?

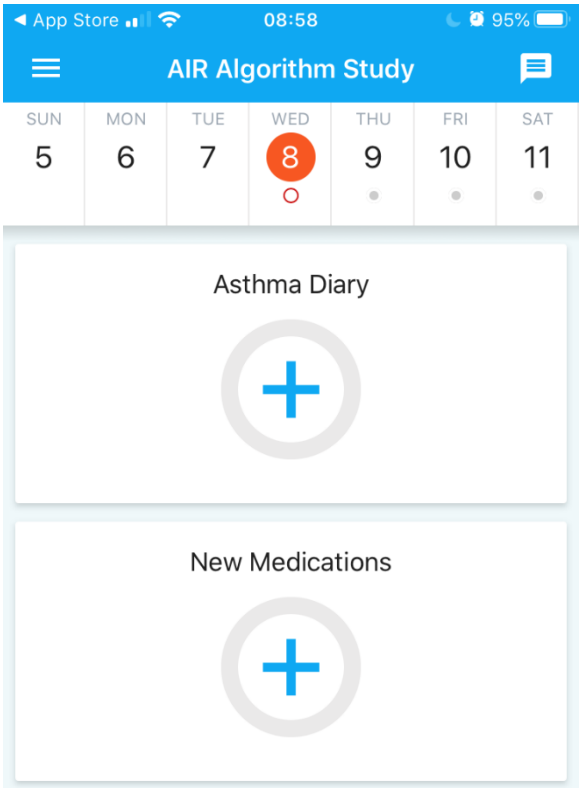


1.1.3 Instructions

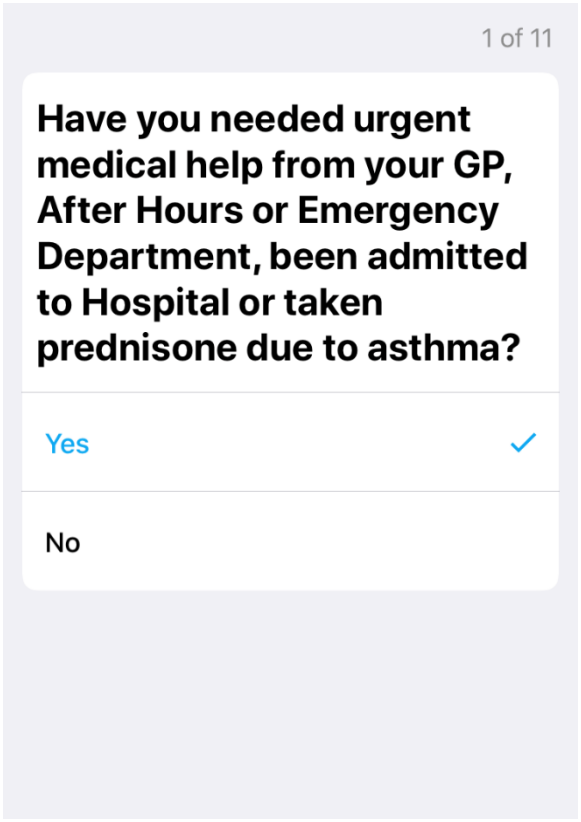
1.1.4 Asthma plan



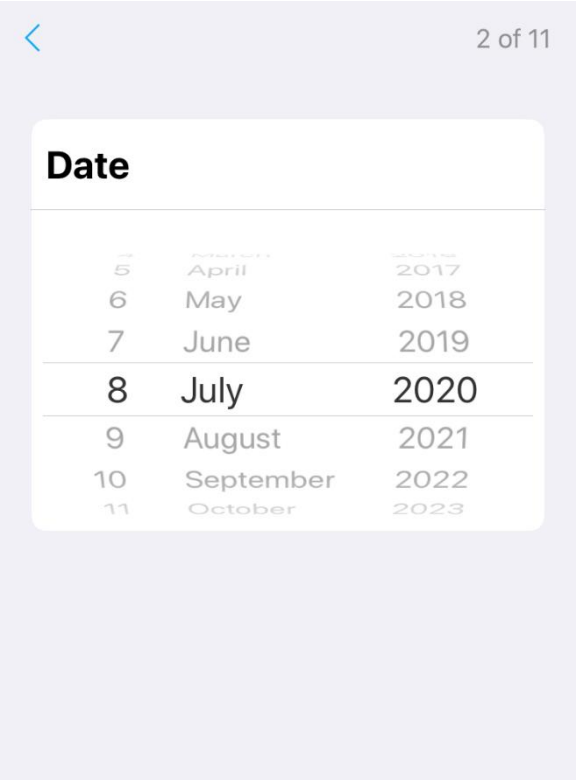
1.2. Main Page



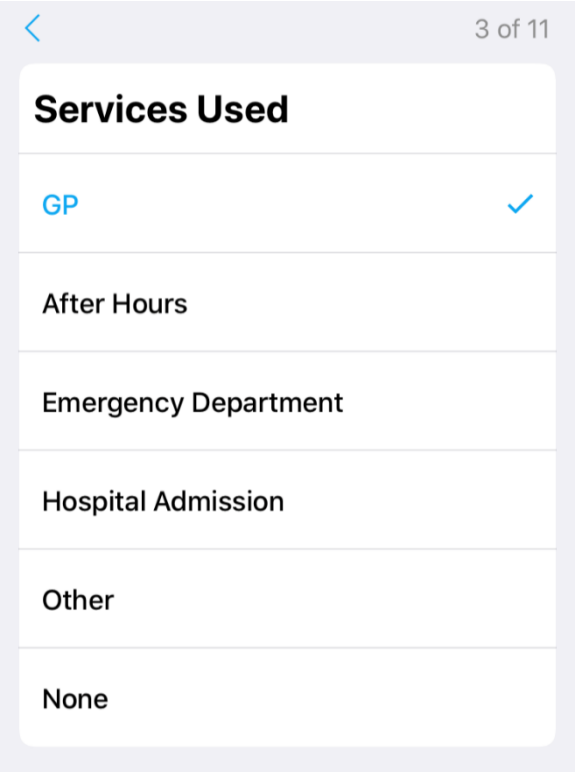
1.2.1.1. Asthma diary



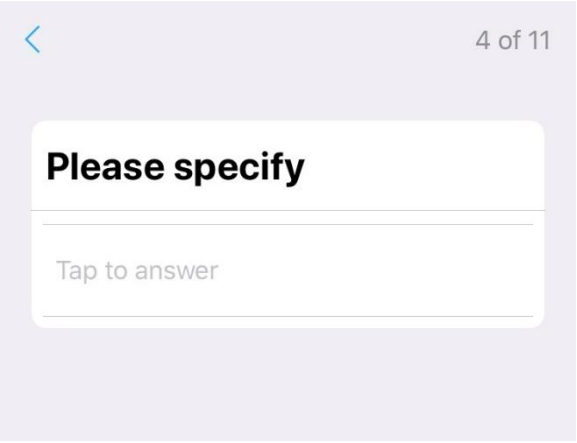
1.2.1.2. Asthma diary



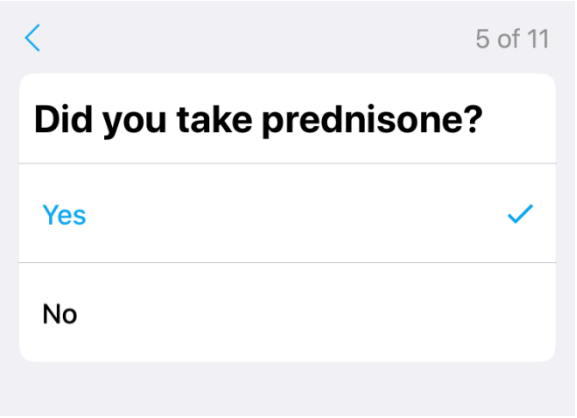
1.2.1.3. Asthma diary



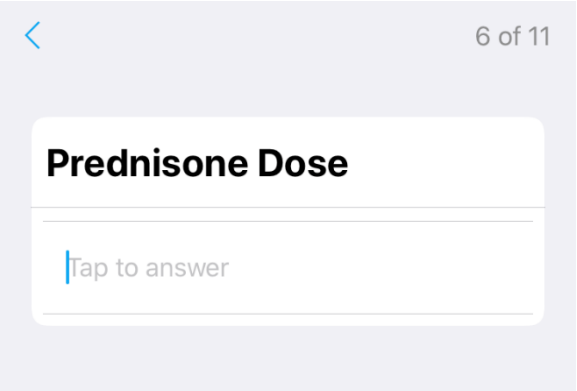
1.2.1.4. Asthma diary (only if 'Other' in 1.2.1.3.)



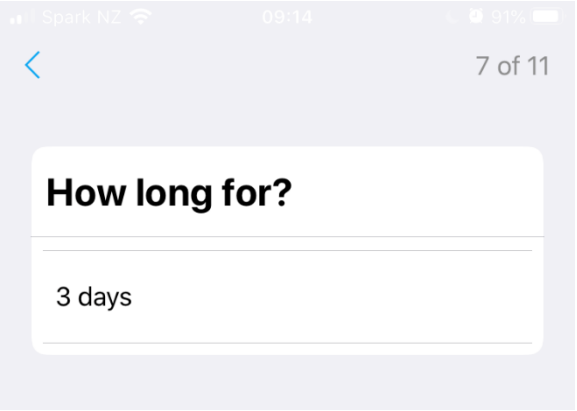
1.2.1.5. Asthma diary



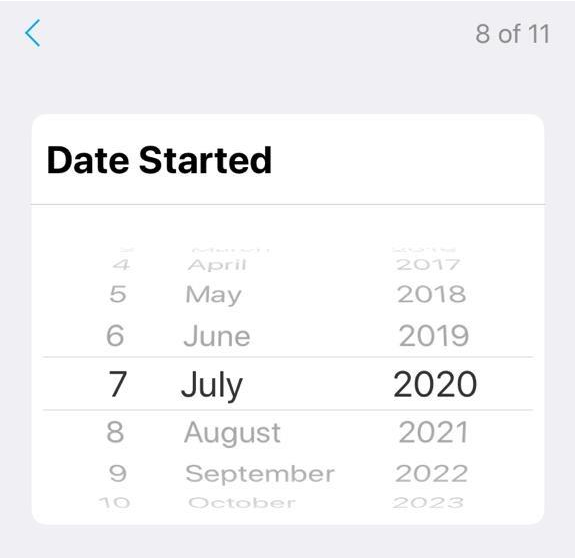
1.2.1.6. Asthma diary



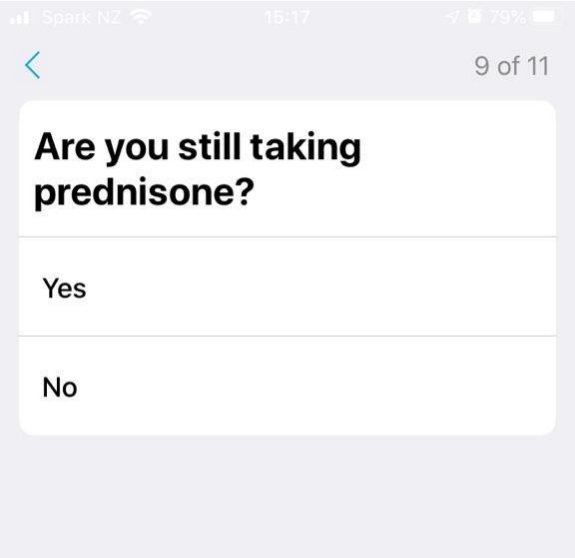
1.2.1.7. Asthma diary



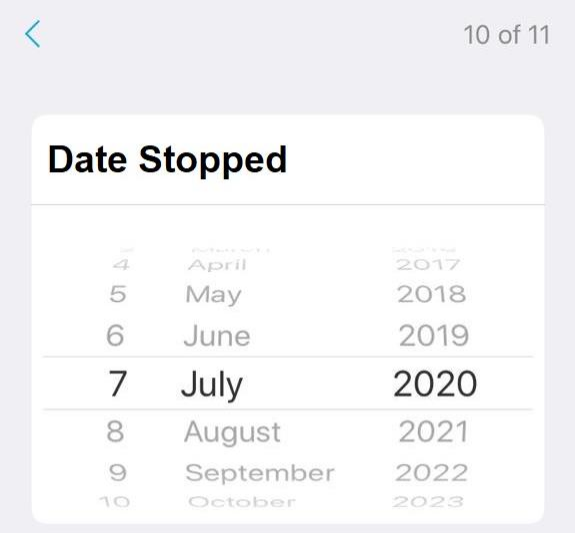
1.2.1.8. Asthma diary



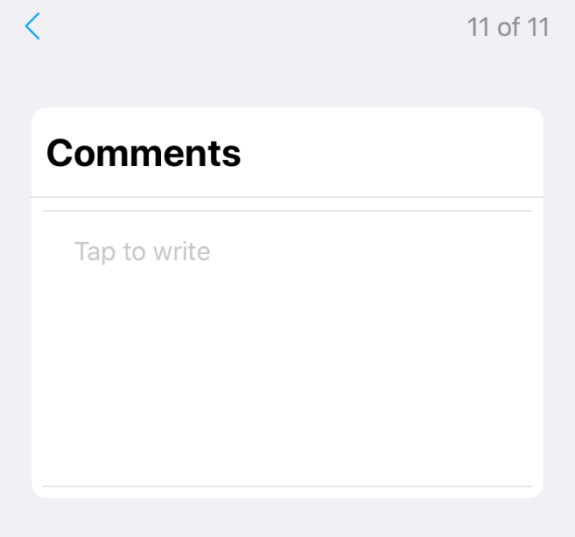
1.2.1.9. Asthma diary



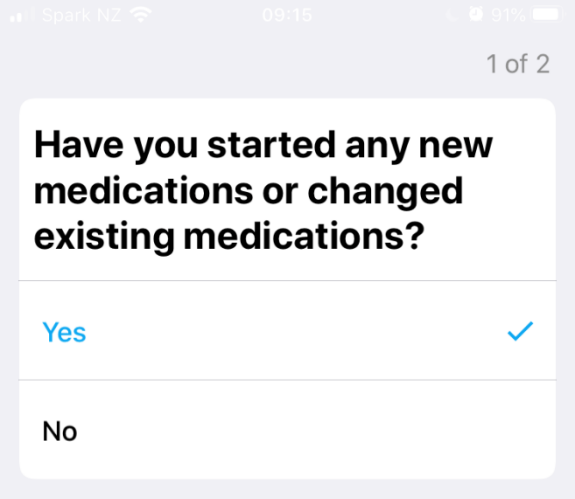
1.2.1.10. Asthma diary (only if "No" in 1.2.1.9.)



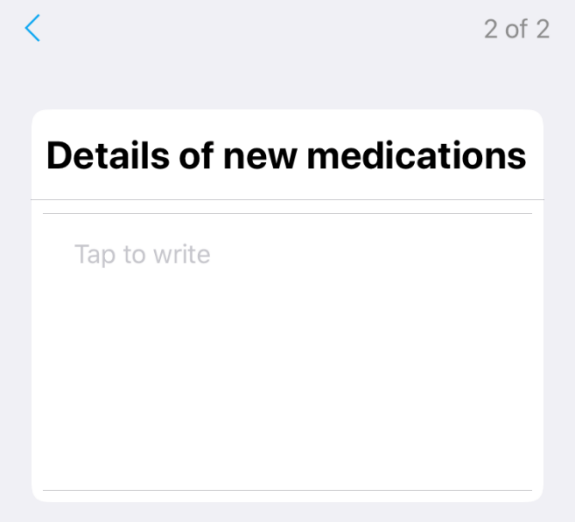
1.2.1.11. Asthma diary



1.2.2.1. New Medications



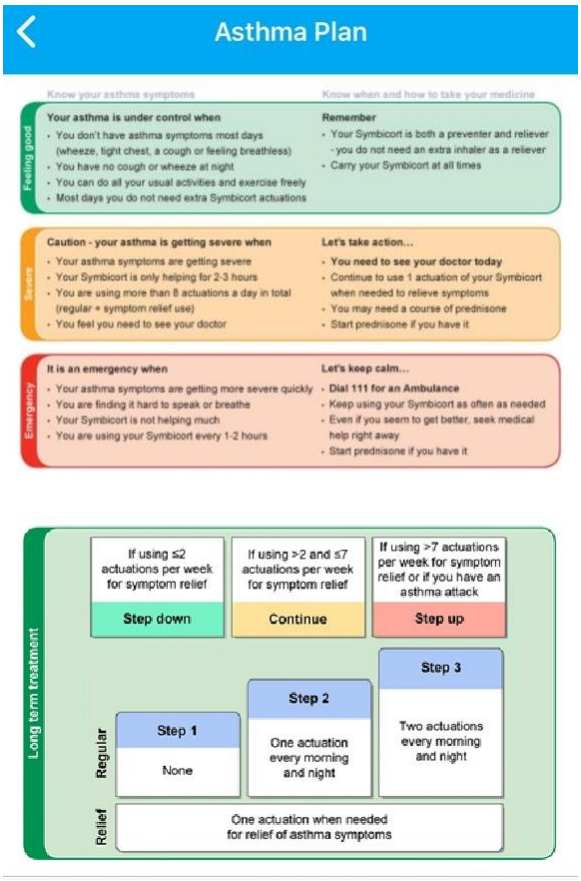
1.2.1.2. New Medications (only if "Yes" in 1.2.2.1.)



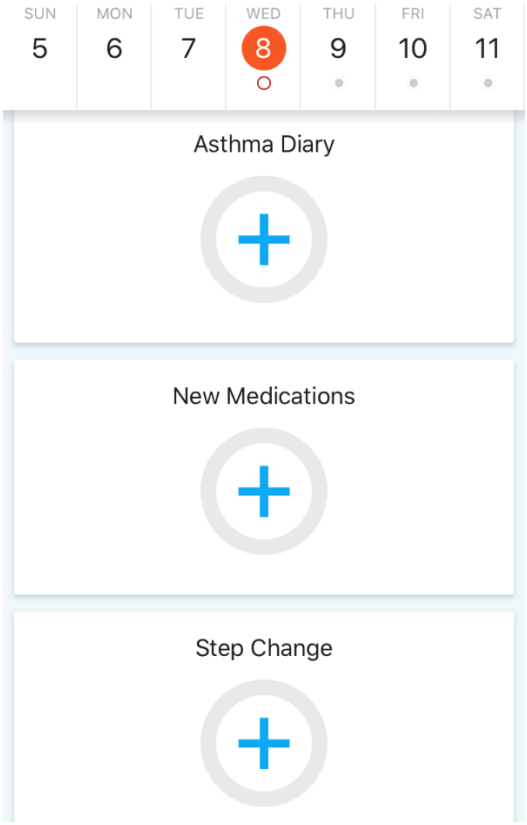
Phase Two MyCap Screenshots (only changes to Phase One screenshots highlighted)

2.1.2.1 When to contact the Investigator (instead of 1.1.2.1)

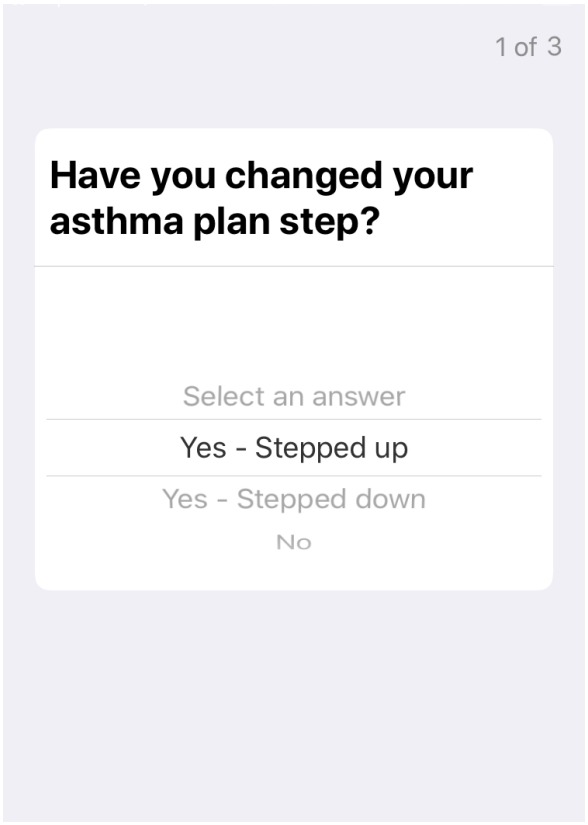
2.1.4 Asthma plan (instead of 1.1.4)



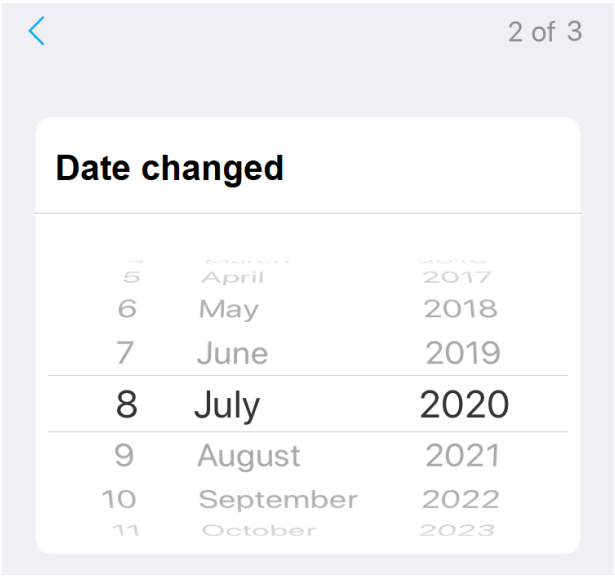
2.2. Main Page (instead of 1.2)



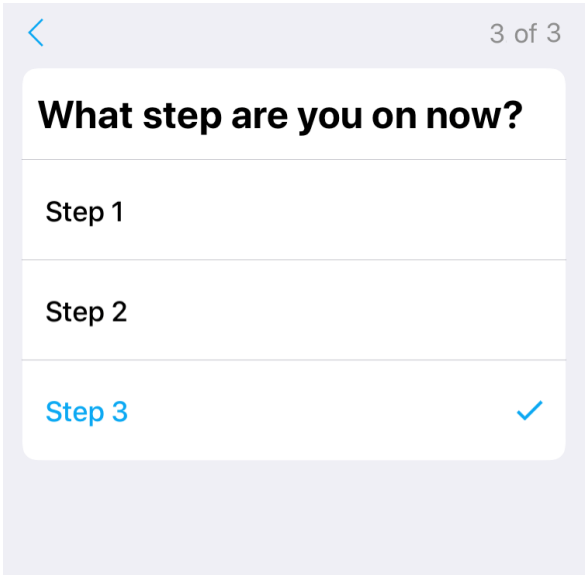
2.2.3.1 Step change (new)



2.2.3.2 Step change (if "Yes" in 2.2.3.1)



2.2.3.3 Step change



APPENDIX E: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	V1.0	09/07/2020	N/A	N/A
1	V1.1	10/09/2020	PB	AZ Safety Information added ACT updated to Australian version Schedule of Procedures updated
2	V2.0	28/09/2020	PB	Exclusion criteria clarified to exclude recent use of "unapproved medicines" ACT updated to include NZ brand names
3	V2.1	14/12/2020	PB	Appendix A Figure 3: Low, Medium and High Daily Dose of Inhaled Corticosteroids added
4	V2.2	09/03/2021	PB	Schedule of Procedure updated
5	V2.3	30/03/2021	PB	ACTRN for Tutorial substudy on first page - corrected
6	V2.4	29/04/2021	PB	Proportion of participants recruited changed to 25 from each of the first 4 GINA 2018 treatment steps
7	V2.5	29/07/2021	PB	Clarification that TSQM should be administered in case of unscheduled visit for treatment discontinuation or study withdrawal.
8	V2.6	21/04/2022	PB	List of Investigators updated Primary outcome name corrected to Global satisfaction (same outcome but name changed from Overall satisfaction in TSQM version I to Global satisfaction for version II) Outcomes and statistical analysis updated to better reflect the Statistical Analysis Plan v1.0. Inclusion of carbon footprint analysis