Statistical Analysis Plan

Study Title	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

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1. ADMINISTRATIVE INFORMATION

1.1. Protocol Version

This document has been written based on information contained in the study protocol MRINZ/19/13 Version 2.6 (21/04/2022).

1.2. Author Information

Author name and title	Signature	Date
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1.3. Reviewer Information

Reviewer name and title	Role	Affiliation
Dr Irene Braithwaite	Protocol Author, Investigator	Medical Research Institute of New Zealand
Mr Mark Holliday	Protocol Author, Monitor	Medical Research Institute of New Zealand

2. 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
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
NZ	New Zealand
SABA	Short-Acting Beta-Agonist
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
TSQM	Treatment Satisfaction Questionnaire for Medication

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

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.

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 is defined as >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.

Marked Overuse of Inhaler is defined as >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.

3. STUDY DETAILS

3.1. 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 1: Week 0 to Week 26 Phase 2: 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

3.2. 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. 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. 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. 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. 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. 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.

3.3. Objectives

The trial will be conducted in two phases: Phase 1 Analysis will take place after Visit 3 (Week 1 to Week 26) and Phase 2 extends to Visit 5 (Week 52).

Outcomes denoted by an * will be presented i) by AIR Algorithm treatment step at baseline and ii) by participants that have remained on the same treatment step, stepped up or stepped down their study treatment on entry to each visit (see section 6.1 for further details).

3.3.1. Outcome Measures at Completion of Phase 1

Objectives	Outcome Measures	Timepoint(s)
Participant satisfaction	• Individual scores for each domain of the TSQM (effectiveness, convenience, side effects, global satisfaction)*	Visits 1, 2 & 3
	• Participant preference scores	Visit 3
Flow through treatment steps	• Number of participants on each treatment step	Visit 1, 2 & 3
	• Number of participants that change treatment step	Visit 1, 2 & 3
Effectiveness	• ACT Score*	Visit 1 & 3
	• ACQ-5 Score*	Visit 1 & 3
	• AQLQ-S Score*	Visit 1 & 3
	• On-treatment FEV_1*	Visit 1 & 3
	• FeNO*	Visit 1 & 3
	• Number and rate of severe exacerbations	Visit 3
	• Number and rate of moderate and severe exacerbations	Visit 3
	• Proportion of participants withdrawn and treatment discontinued and reason	Visit 3
Patterns of medication use	• Mean ICS dose per day (budesonide µg/day)*	Visit 2 & 3
	• Mean β-agonist dose per day (formoterol µg/day)*	Visit 2 & 3
	• Proportion of participants requiring other asthma related medications	Visit 3
	• Longest duration of no actuations (days)*	Visit 2 & 3
	• Proportion of days of no inhaler use*	Visit 2 & 3
	• Number of days of high inhaler use*	Visit 2 & 3
	• Number of days of marked inhaler overuse*	Visit 2 & 3

	• Proportion of high inhaler use episodes without medical review within 48hr	Visit 2 & 3
	• Proportion of marked inhaler overuse episodes without medical review within 48hr	Visit 2 & 3
Safety	• Adverse events	Visit 3
	• Proportion with at least 1 related AE	Visit 3
	• Serious adverse events	Visit 3
	• Proportion with at least 1 related SAE	Visit 3

3.3.2. Outcome Measures at Completion of Phase 2

Objectives	Outcome Measures	Timepoint(s)
Participant satisfaction	• Individual scores for each domain of the TSQM (effectiveness, convenience, side effects, global satisfaction)*	Visit 3, 4 & 5
	• Participants preference scores	Visit 5
Participant flow through treatment steps	• Number of participants on each treatment step	Visit 3, 4 & 5
	• Number of participants that change treatment step	Visit 3, 4 & 5
	• Self-reported number of times participant changed treatment step	Visit 4 & 5
	• Proportion of participants that qualified for a treatment step change	Visit 5
	• Proportion of participants that qualified for a treatment step change and declined	Visit 5
	• Participant led treatment step changes +/- 14 days of an asthma attack	Visit 5
Effectiveness	• ACT Score*	Visit 3 & 5
	• ACQ-5 Score*	Visit 3 & 5
	• AQLQ-S Score*	Visit 3 & 5
	• On-treatment FEV_1*	Visit 3 & 5
	• FeNO*	Visit 3 & 5
	• Number and rate of severe exacerbations	Visit 5
	• Number and rate of moderate and severe exacerbations	Visit 5
	• Proportion of participants withdrawn and treatment discontinued and reason	Visit 5
Patterns of medication use	• Mean ICS dose per day (budesonide µg/day)*	Visit 4 & 5
	• Mean β-agonist dose per day (formoterol µg/day)*	Visit 4 & 5
	• Proportion of participants requiring other asthma related medications	Visit 5
	• Longest duration of no actuations (days)*	Visit 4 & 5
	• Proportion of days of no inhaler use*	Visit 4 & 5
	• Number of days of high inhaler use*	Visit 4 & 5

	• Number of days of marked inhaler overuse*	Visit 4 & 5
	• Proportion of high inhaler use episodes without medical review within 48hr	Visit 4 & 5
	• Proportion of marked inhaler overuse episodes without medical review within 48hr	Visit 4 & 5
Safety	• Adverse events	Visit 5
	• Proportion with at least 1 related AE	Visit 5
	• Serious adverse events	Visit 5
	• Proportion with at least 1 related SAE	Visit 5
Participant beliefs about medicines	• BMQ SABA scores (Necessities and Concerns)	Visit 1, 3 & 5
	• BMQ AIR score (Necessities and Concerns)	Visit 1, 3 & 5
Carbon footprint	• Carbon footprint as carbon dioxide-equivalent (CO_2e) emissions per person year	Visit 5

3.4. Study Design

This is a prospective, single centre, interventional, open label, single group study of a novel asthma treatment algorithm 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.

3.5. Sample Size

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.

3.6. Timing of Analyses

The trial analyses will be conducted in two phases: following the completion of Phase 1 (Week 26) and Phase 2 (Week 52).

3.6.1. Phase 1

All Phase 1 outcomes will be analysed after completion of:

- The last participant visit 3

This will include calculation of the minimal clinically important difference (MCID) for the Global Satisfaction score of the TSQM vII will be estimated in relation to ACT, ACQ-5, AQLQ-S and FEV_1.

3.6.2. Phase 2

All Phase 2 and overall outcomes will be analysed after completion of:

- The last participant last visit (LPLV)

4. STATISTICAL PRINCIPLES

4.1. The Level of Statistical Significance

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

4.2. Adherence and Protocol Deviations

In order to more closely mimic clinical use in clinical practice, compliance with the intervention will be encouraged through participant education but it will not be recorded.

A protocol deviation is defined as failure to adhere to the protocol, such as incorrect data being collected and documented, errors in applying inclusion/exclusion criteria, or missed follow-up visits. Reasons for deviation will be categorised as:

- Enrolment process (inclusion/exclusion criteria, recruitment, etc.)
- Consent process (oral or written)
- Study Intervention (dose error, incorrect administration, etc.)
- Equipment (malfunction, calibration, etc.)
- Data Management (data analysis, reporting, storage, etc.)
- General Protocol Compliance (adherence to specified visit windows, procedures, etc.)
- Other (to be stated)

A potential participant who was enrolled but who did not meet the inclusion and exclusion criteria will be deemed ineligible, and not included as part of the analysis data set. On occasions a participant may only be identified as ineligible during follow up. If this is the case, no measurements from the ineligible participant will be included in the data set.

Reasons for deviations will be summarised as above. Other minor deviations from protocol (not affecting the study results) may be recorded during the study. These will not be formally presented either to the DSMC or in the final report, however they will be checked and recorded as part of study monitoring. These include but are not limited to missing data from incomplete assessments.

A protocol violation is defined as one affecting the efficacy, the safety, physical or mental integrity of the participants in the trial, or the scientific value of the trial. The number (and proportion) of participants with major and minor protocol deviations will be summarised with details of the type of deviation provided. The participants that are included in the safety dataset will be used as the denominator to calculate the proportions.

4.3. Analysis Populations

4.3.1. Analysis Dataset

For calibration of the TSQM Global Satisfaction MCID, the analysis dataset will include all participants enrolled up until the point of withdrawal, unless as described above, 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 completion date because it cannot be assumed that their subsequent data will be missing at random.

4.3.2. Safety Dataset

For the purpose of adverse event reporting and analysis, the safety data set will include all participants who received at least one dose of study medication.

5. TRIAL POPULATION

5.1. Screening Data

A CONSORT diagram will be used to report enrolment, treatment discontinuation and withdrawal data in line with CONSORT guidelines. Eligibility criteria are listed in the protocol (section 7), but briefly participants are adults aged 18 to 75 years with self-reported doctor diagnosed asthma for which they use a SABA reliever, ICS maintenance plus a SABA reliever, or ICS/LABA maintenance plus a SABA reliever.

5.2. Treatment Discontinuation/ Withdrawal

The CONSORT diagram will report the primary reason for treatment discontinuation and withdrawal as one of the following:

5.2.1. Treatment Discontinuation

- Pregnancy
- Ineligibility (either arising during the trial or determined in retrospect)
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Significant protocol deviation
- Withdrawal of consent for treatment
- Other (to be stated)

5.2.2. Withdrawal

- Withdrawal of consent for participation
- Other (to be stated)

5.3. Baseline Participant Characteristics

5.3.1. History

- Sex
- Ethnicity
- Age (years)
- Age of asthma diagnosis
- TSQM score
- ACQ-5 score
- AQLQ
- ACT score
- BMQ-AIR (phase 2 only)
- BMQ-SABA (phase 2 only)
- Severe asthma attack in the past 12 months,
- Number of severe asthma attacks in the past 12 months in those that had at least one
- Smoking status
- Pack years
- Number of previous ED visit for asthma requiring systemic corticosteroids in the last year
- Number of hospital admissions for asthma in the last year
- GINA treatment step (2018 criteria)
- Asthma Medications
    - Whether the participant currently uses SABA reliever therapy with a breakdown of medication categories
    - Whether the participant currently uses SABA monotherapy with a breakdown of medication categories
    - Whether the participant currently uses ICS only maintenance therapy with a breakdown of medication categories
    - Whether the participant currently uses ICS/LABA maintenance therapy with a breakdown of medication categories

5.3.2. Measurements

- BMI
- Best FEV1
- Best FEV1 % predicted
- Best FVC
- FeNO (ppb)

Baseline characteristics of participants who were lost to follow up following visit 1, and so provided no follow up data, will be summarised in an additional table within the supplementary appendix.

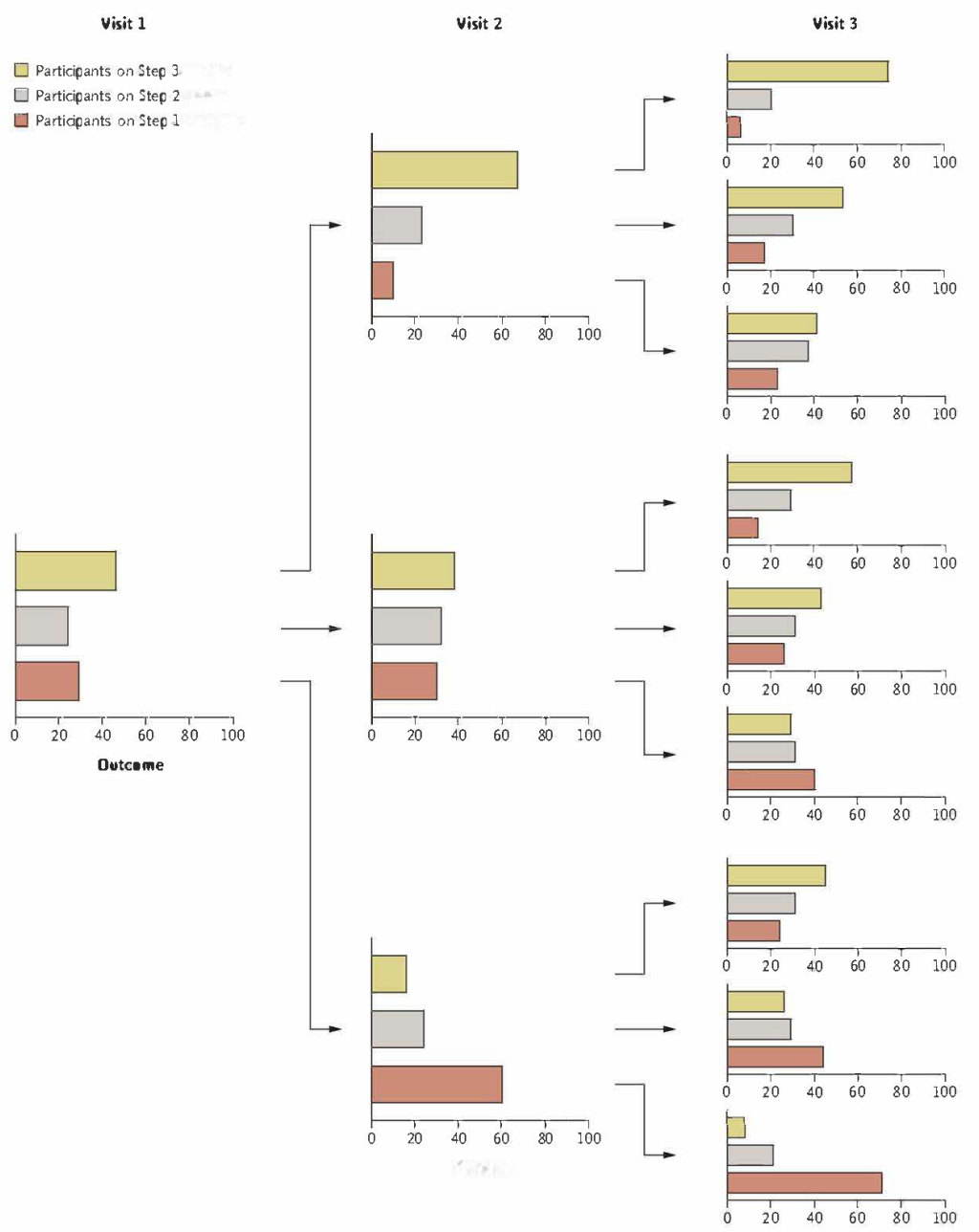
6. STATISTICAL ANALYSIS

6.1. Data Description for All Outcome Variables

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.

Outcomes denoted by an * will also be presented i) by AIR Algorithm treatment step at baseline and ii) by participants that have remained on the same treatment step, stepped up or stepped down their study treatment on entry to each visit (as illustrated in Fig 1).

Fig 1: Example figure to demonstrate assessment based on treatment steps at timepoints



The proportion of participants on each treatment step and proportion of participants that change treatment step will be displayed by Alluvial plots, including an initial node for GINA step at baseline followed by AIR Algorithm Step at Visit 1 and subsequent visits.

Adverse and serious adverse events will be summarised by the overall number of AE/SAEs and the proportion of participants with at least 1 AE/SAE related to the IMP.

Net asthma carbon footprint per participant, expressed as carbon dioxide equivalents (CO_2e), 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.

6.1.1. Phase 1 Analysis

Primary Analysis	**Baseline**	**Timepoint**
• Change in TSQM Global Satisfaction Score	Visit 1	Visit 3

The primary analysis of the primary outcome will be by paired t-test, with associated confidence interval.

TSQM Global Satisfaction Scores 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.

Secondary Analyses

MCID calibration

• The minimal clinically important difference (MCID) for the Global Satisfaction domain of the TSQM	Visit 1	Visit 3

Estimate the MCID for TSMQ Global Satisfaction scores, 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 1, to estimate the equivalent change.

- Primary analysis for estimating the MCID of the TSQM Global Satisfaction scores using a regression approach to scores against ACQ-5 scores.
- Secondary analysis for estimating the MCID of the TSQM Global Satisfaction scores will take a similar approach for AQLQ-S, ACT, and FEV_1.

Table 1: Minimal clinically important difference for ACT, ACQ-5, AQLQ-S and FEV_1.

Instrument	**Minimal clinically important difference**
ACQ-5 scores	0.5 points
AQLQ-S scores	0.5 points
ACT scores	3 points
FEV_1 measures	230 ml

Paired t-test

• Change in ACT Score	Visit 1	Visit 3
• Change in ACQ-5 Score	Visit 1	Visit 3
• Change in AQLQ-S Score	Visit 1	Visit 3
• Change in On-treatment FEV_1	Visit 1	Visit 3
• Change in FeNO^	Visit 1	Visit 3

^FeNO scores and change from baseline will be reported 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.

Other

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.

6.1.2. Phase 2 Analysis

Primary Analysis	**Baseline**	**Timepoint**
• Change in TSQM Global Satisfaction Score	Visit 3	Visit 5
• Change in TSQM Global Satisfaction Score	Visit 1	Visit 5

The primary analysis of the primary outcome will be by paired t-test, with associated confidence intervals.

TSQM Global Satisfaction Scores 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.

Secondary Analyses

Regression

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

Paired t-test

• Change in ACT Score	Visit 3	Visit 5
• Change in ACT Score	Visit 1	Visit 5
• Change in ACQ-5 Score	Visit 3	Visit 5
• Change in ACQ-5 Score	Visit 1	Visit 5
• Change in AQLQ-S Score	Visit 3	Visit 5
• Change in AQLQ-S Score	Visit 1	Visit 5
• Change in on-treatment FEV_1	Visit 3	Visit 5
• Change in on-treatment FEV_1	Visit 1	Visit 5
• Change in FeNO^	Visit 3	Visit 5
• Change in FeNO^	Visit 1	Visit 5
• Change in mean ICS dose per day (budesonide µg/day)	Visit 3	Visit 5
• Change in mean β-agonist dose per day (formoterol µg/day)	Visit 3	Visit 5
• Change in longest duration of no actuations (days)	Visit 3	Visit 5
• Change in number of days of high inhaler use	Visit 3	Visit 5
• Change in number of days of marked inhaler overuse	Visit 3	Visit 5
• Change in inhaler use over -7 days of treatment step up and +7 days of treatment step up	7 days pre-event	7 days post-event
• Change in inhaler use over -7 days of treatment step up and +7 days of treatment step down	7 days pre-event	7 days post-event

^FeNO scores and change from baseline will be reported 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.

McNemar's test

• Change in proportion of days of no inhaler use	Visit 3	Visit 5

Poisson regression with an offset for number of days in the study

• Change in number and rate of severe exacerbations	Pre-12m	Visit 5
• Change in number and rate of moderate and severe exacerbations	Pre-12m	Visit 5

Other

- 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.
- Difference between participant reported inhaler use and electronic monitor recorded use at visits 2, 3, 4 and 5 will be explored by Bland-Altman plots and limits of agreement.

6.2. 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.

7. QUALITY ASSURANCE PROCEDURES

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

APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	V1.0	21/04/2022	N/A	N/A