The Anti-Inflammatory Reliever (AIR) Algorithm Study: a protocol for a single-group study of an AIR stepwise approach to the treatment of adult asthma

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Shareable abstract (@ERSpublications)
This protocol describes the first trial to investigate the anti-inflammatory reliever stepwise track for the management of adult asthma, utilising a pragmatic algorithm for transitioning between steps, and providing much needed knowledge on this approach https://bit.ly/44x11Eh

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Abstract

Background The stepwise approach to long-term asthma management, which traditionally incorporates short-acting β_2-agonist reliever therapy, has been a core feature of asthma guidelines for over 30 years. There have been no studies, however, directly investigating the use of an entire guideline-recommended track. Recently, inhaled corticosteroid–formoterol has been recommended as the preferred reliever therapy in adult asthma, in accordance with a stepwise "Anti-Inflammatory Reliever" (AIR) treatment track.

Objective The aim of this study was to evaluate the AIR stepwise approach recommended by the New Zealand adolescent and adult asthma guidelines, in combination with a novel algorithm for transitioning between treatment steps.

Methods This 52-week, open-label, single-group study will recruit 100 adults aged 18 to 75 years with mild, moderate and moderate–severe asthma (ACTRN12620001010987). Participants will be allocated to budesonide–formoterol 200/6 µg, one actuation as needed (Step 1), one actuation twice daily and as needed (Step 2), or two actuations twice daily and one as needed (Step 3). Treatment steps will be adjusted throughout the study, in response to reliever use and asthma attacks, according to a stepwise AIR algorithm. Following a 26-week period of investigator-led transitions, participants will adjust their own treatment step. The primary outcome is participant satisfaction as measured by the Global Satisfaction score of the Treatment Satisfaction Questionnaire for Medication. Secondary outcomes will assess efficacy and safety, and describe patterns of medication use and participant flow through the treatment steps.

Conclusion This is the first trial to assess the AIR treatment track and algorithm. The results will provide knowledge to guide the clinical use of this approach.

Introduction

Background and rationale

Since publication of the first Global Initiative for Asthma (GINA) report in 1995 [1], the stepwise approach to the pharmacological treatment of asthma has become a key feature of international and national asthma guidelines [2–6]. This concept recommends that patients are prescribed a short-acting β_2-agonist (SABA) for symptom relief (and prior to exercise), together with maintenance asthma treatment, the intensity of which is increased or decreased according to changes in asthma control and exacerbation risk. The various steps are outlined in a treatment "track", versions of which have evolved over the decades

in terms of the maintenance treatment recommended at the different treatment steps, taken together with SABA reliever therapy. To the best of our knowledge, there have been no detailed investigations of the utility of any of the specific stepwise tracks that have been recommended since 1995.

The GINA 2019 update recommended that low-dose inhaled corticosteroid (ICS)–formoterol is preferred to a SABA as reliever therapy, across the spectrum of asthma severity, in adults and adolescents [7]. This approach was incorporated in a stepwise track, together with the option of SABA reliever therapy. In 2020 the Asthma and Respiratory Foundation New Zealand adolescent and adult asthma guidelines took the novel approach of proposing two separate treatment tracks, in which the preferred track was based on budesonide–formoterol reliever therapy, referred to as the Anti-Inflammatory Reliever (AIR) track, and the alternative track was based on SABA reliever therapy [8]. During the 18-month period after the publication and dissemination of the 2020 New Zealand asthma guidelines, there was a progressive and substantial increase in budesonide–formoterol dispensing, accompanied by a reduction in dispensing of SABA and other ICS long-acting β-agonist (LABA) medications [9]. In 2021 GINA similarly proposed separate tracks and recommended that the low-dose ICS–formoterol reliever-based track was preferred over the SABA counterpart [10].

Based on comparisons between the two reliever regimens at each step of the respective tracks, the ICS–formoterol-based track would be expected to have greater efficacy due to reduced severe exacerbation risk, and a better safety profile due to both reduced systemic corticosteroid-related adverse effects and reduced risk of reliever overuse episodes leading to delay in seeking medical review [11–16].

A key issue with the implementation of the proposed tracks is how patients transition between the different steps in response to changes in asthma symptom control and exacerbations. For the New Zealand asthma guidelines an AIR algorithm has been proposed that provides clear numerical cut-off points for transitioning between treatment steps, initially allowing for doctor-led and subsequently participant-led step changes, following a period of education [17, 18].

Unique in considering the utility of, and participant engagement with, all steps of an asthma treatment track and a novel algorithm for transitioning between steps, this proof-of-concept study will seek to provide a comprehensive assessment of the AIR track and algorithm in clinical practice.

Objective

The primary objective is to estimate participant satisfaction with the AIR stepwise track and algorithm approach to the pharmacological treatment of asthma in adults aged 18 to 75 years across the spectrum of asthma severity. Secondary objectives include estimating the association between satisfaction, as estimated by Global Satisfaction score of the Treatment Satisfaction Questionnaire for Medication, and the Asthma Control Questionnaire (ACQ-5), and to nominate a minimum clinically important difference (MCID) for the former based on the regression coefficient related to a 0.5-unit change on the ACQ-5.

Methods

Study design

The AIR Algorithm Study is an investigator-initiated, 52-week, single-site, open-label, single-group trial based in New Zealand. It is funded by the Medical Research Institute of New Zealand (MRINZ) which receives Independent Research Organisation funding from the Health Research Council of New Zealand (IRO grant [18/002]).

AstraZeneca Ltd is providing support for this research by supply of the study medication (Symbicort Turbuhaler®, AstraZeneca Ltd, Cambridge, UK), electronic monitors (Turbu+™, Adherium Ltd, Auckland, New Zealand) and funding to support electronic monitor data collection (Hailie®, Adherium Ltd). AstraZeneca has no role in designing the study; writing the protocol; data collection, analysis, and interpretation; or in the decision to submit manuscripts for publication.

The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12620001010987). It was approved by the Central Health and Disability Ethics Committee (20/CEN/154). The date of first participant enrolment and last data collection was December 2020 and July 2022, respectively. The estimated date of database lock and statistical analysis is July 2023.

Participants and recruitment

100 participants aged 18 to 75 years with doctor-diagnosed asthma, and current use of a SABA reliever, with or without regular maintenance ICS or ICS-LABA therapy, will be recruited at the MRINZ based in

Wellington, New Zealand. Participants will be identified from the MRINZ clinical trial database, general practice mailouts and direct advertising. Potentially eligible volunteers will be invited to attend an initial screening visit. Written informed consent is required before any trial-specific procedures are performed.

Interventions

Eligible participants (table 1) will be allocated to the appropriate AIR treatment track step (figure 1a), based on their current prescribed treatment regimen (table 2):

Step 1: ICS-LABA reliever: budesonide–formoterol 200/6 µg dry powder inhaler (DPI) (Symbicort Turbuhaler®, AstraZeneca), one actuation as required to relieve symptoms.

Step 2: Low-dose ICS-LABA single maintenance and reliever therapy (SMART): budesonide–formoterol 200/6 µg DPI, one actuation twice daily and ICS-LABA reliever: budesonide–formoterol 200/6 µg DPI, one actuation as required to relieve symptoms.

Step 3: Medium-dose ICS-LABA SMART: budesonide–formoterol 200/6 µg DPI, two actuations twice daily and ICS-LABA reliever: budesonide–formoterol 200/6 µg DPI, one actuation as required to relieve symptoms.

During Phase 1 (the first 26 weeks of the study), investigators will assess the allocated study treatment step at 13-week intervals and determine whether the participant 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 (figure 1b), this will be based on participant-reported average weekly reliever use, and whether the participant experienced an asthma attack, since the last study visit. For this study an asthma attack is defined as a deterioration in asthma symptoms severe enough to warrant the use, or prescription,

TABLE 1 Eligibility criteria

Inclusion criteria	Exclusion 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 Regular oral corticosteroids • 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	• 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 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 2 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 >20 pack-years smoking history, or onset of respiratory symptoms after the age of 40 years in current or ex-smokers with ⩾10 pack-years history • Self-reported current pregnancy or breastfeeding 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 • A body mass index of ⩾40 kg·m^{-2} • 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

SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; ICU: intensive care unit.

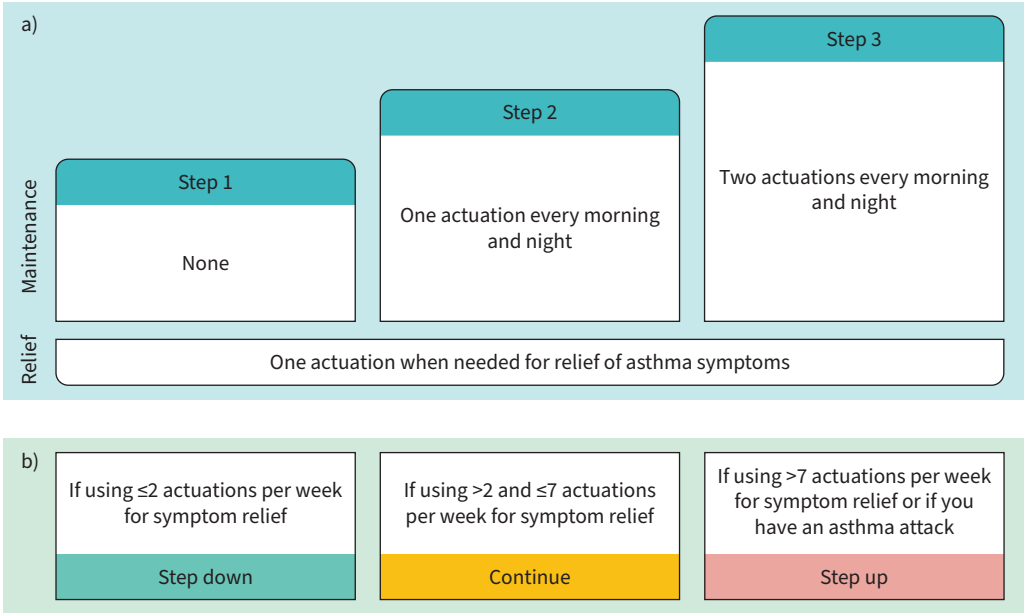

FIGURE 1 The Anti-Inflammatory Reliever (AIR) stepwise treatment track and participant-facing algorithm. a) The AIR stepwise treatment track based on the combination budesonide–formoterol 200/6 µg dry powder inhaler. b) The AIR algorithm.

of systemic corticosteroids, such as a course of prednisone. Participants who meet the criteria to be stepped-up beyond Step 3 of the AIR treatment track during any point of the 12-month period will be referred for specialist respiratory review at study completion.

During Phase 2 (from week 26 to week 52), participants will be provided with an asthma action plan outlining how to self-adjust their treatment step in accordance with the AIR algorithm, starting with monthly self-reviews for 3 months, after which they will be encouraged to adjust their treatment as often as they feel necessary.

TABLE 2 Determination of treatment step at enrolment

Treatment step pre-enrolment[#]	AIR treatment step at enrolment
GINA Step 1: SABA monotherapy	**Allocate to Step 1:** ICS–LABA reliever: budesonide–formoterol 200/6 µg DPI, one actuation as required to relieve symptoms
GINA Step 2: Low-dose ICS plus SABA reliever **GINA Step 3:** Medium- or high-dose ICS plus SABA reliever **or** Low-dose ICS–LABA plus SABA reliever	**Allocate to Step 2:** Low-dose ICS–LABA maintenance: budesonide–formoterol 200/6 µg DPI, one actuation twice daily **and** ICS–LABA reliever: budesonide–formoterol 200/6 µg DPI, one actuation as required to relieve symptoms
GINA Step 4: Medium- or high-dose ICS–LABA plus SABA reliever	**Allocate to Step 3:** Medium-dose ICS–LABA maintenance: budesonide–formoterol 200/6 µg DPI, two actuations twice daily **and** ICS–LABA reliever: budesonide–formoterol 200/6 µg DPI, one actuation as required to relieve symptoms

GINA: Global Initiative for Asthma; SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; DPI: dry powder inhaler. [#]: based on prescribed treatment used in the last 3 months, with recommended cut-off points for low-, medium- and high-dose ICS as outlined in the GINA 2018 guidelines.

Outcome measures

The primary outcome is participant satisfaction as measured by the Global Satisfaction score of the Treatment Satisfaction Questionnaire for Medication (TSQM v.II) [19]. The TSQM consists of 11 questions representing four domains (effectiveness, side-effects, convenience and global satisfaction) relating to medication in the setting of chronic disease. At week 26, the MCID of the Global Satisfaction domain of the TSQM will be calculated, with a regression approach, to estimate the size of domain scores change in relation to the MCID of the ACQ-5 scores. A 0.5-unit change in ACQ-5 represents a clinically important change [20, 21].

Secondary outcomes measures (table 3) will assess the safety and efficacy of the AIR treatment track and algorithm across the 52-week study course, including asthma exacerbations defined as per the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines [22]. Transitions between the treatment steps will also be analysed, along with consideration of the net carbon footprint per participant associated with study treatment.

Trial procedures

Participants will attend five in-person visits during the 52-week study course (see table 4 and supplementary figure S1). Treatment satisfaction will be assessed at each of these time points by the TSQM administered electronically. The ACQ-5, Asthma Quality of Life Questionnaire (AQLQ-S) and Asthma Control Test (ACT) will be administered at baseline [23, 24], visit 3 and visit 5, as measures of asthma control and quality of life. The Beliefs about Medicines Questionnaires (BMQ-AIR and BMQ-SABA) [25, 26] will be administered at baseline, visit 3 and visit 5 to assess participant beliefs and attitudes on treatment. At visit 3 and visit 5 participants will also be asked to rate "How did you find your study treatment relative to your previous treatment?" on a 5-point Likert scale.

Forced expiratory volume in 1 s (FEV_1) will be measured using an Easy on-PC® Spirometer (NDD Medical Technologies, Zurich, Switzerland). Trials will be graded according to ATS/ERS criteria for acceptability and repeatability and Global Lung Function Initiative reference ranges will be used [27, 28]. FEV_1 will be assessed at baseline, visit 3 and visit 5 along with fractional exhaled nitric oxide (F_{ENO}) – a marker of airways inflammation. F_{ENO} will be measured using a FeNOBreath® device (Bedfont Scientific, Maidstone, UK), in keeping with ATS guidance [29].

At each visit, participants will be provided with asthma education (including on inhaler technique) and a personalised action plan (figure S2), and will be encouraged to use their asthma action plan booklets to log any asthma-related events and changes in medications whilst taking part in the study. Detailed information on adverse events will also be systematically collected at each visit.

At visit 2 and 3 an investigator-led assessment will be made to determine the appropriate step of the AIR treatment track for individual participants to continue treatment on, as per the AIR algorithm, based on reliever use and asthma attacks. At visit 3 participants will be given instruction in interpreting and using the AIR algorithm to self-adjust their treatment steps independently.

Inhalers will be issued at each visit and all fitted with electronic monitor devices (Turbu+, Adherium Ltd), allowing for accurate recording of actuation doses and timing. Inhaler monitors will only be issued upon successful completion of pre-dispensing quality control checks.

Unscheduled visits may occur in Phase 1 following an asthma attack (requiring escalation of treatment step), or at any time to consider treatment discontinuation, withdrawal or to issue further inhalers at the participant's request.

At study completion, a final investigator-led assessment will be made to determine the most appropriate step of the AIR treatment track for participants to be provided as their post-trial treatment with as needed budesonide–formoterol, along with an AIR Asthma Action Plan in keeping with current New Zealand asthma guidelines.

Sample size

The study will recruit 25 participants from each of the first four GINA 2018 treatment steps [30], 100 participants in total, ensuring a minimum of 25 participants on each AIR treatment step at enrolment. The sample size of 25 participants is chosen to give reasonable precision (based on about 20 degrees of freedom) for estimation of variance in the regression procedures. In addition, a total sample size of 100 gives a precision for estimation of a mean change from baseline of 0.2_{SD}. In the Cohen effect size

TABLE 3 Objectives and outcome measures

Objectives	Outcome measures	Timepoint(s)
Primary		
To assess participant satisfaction with AIR algorithm treatment	Change in TSQM Global Satisfaction Score	Visit 1 *versus* 3 Visit 3 *versus* 5 Visit 1 *versus* 5
Secondary		
To assess participant satisfaction with AIR algorithm treatment	Individual scores for each TSQM domain (effectiveness, convenience, side-effects, global satisfaction)#	Visits 1 to 5
	Participant preference scores	Visit 3 and 5
	MCID for the Global Satisfaction domain of the TSQM	Visit 1 *versus* 3
To assess participant flow through AIR algorithm treatments	Number of participants on each treatment step	Visit 1 to 5
	Number of participants that change treatment step	Visit 2 to 5
	Self-reported number of times participant changed treatment step	Visit 4 and 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	Variable
To assess the effectiveness of AIR algorithm treatment	ACQ-5 score#	Visit 1, 3 and 5
	Change in ACQ-5 score	Visit 1 *versus* 3 Visit 3 *versus* 5 Visit 1 *versus* 5
	AQLQ-S score#	Visit 1, 3 and 5
	Change in AQLQ-S score	Visit 1 *versus* 3 Visit 3 *versus* 5 Visit 1 *versus* 5
	ACT score#	Visit 1, 3 and 5
	Change in ACT score	Visit 1 *versus* 3 Visit 3 *versus* 5 Visit 1 *versus* 5
	On-treatment FEV_1#	Visit 1, 3 and 5
	Change in on-treatment FEV_1	Visit 1 *versus* 3 Visit 3 *versus* 5 Visit 1 *versus* 5
	F_{ENO}#	Visit 1, 3 and 5
	Change in F_{ENO}	Visit 1 *versus* 3 Visit 3 *versus* 5 Visit 1 *versus* 5
	Number and rate of severe exacerbations	Visit 3 and 5
	Change in number and rate of severe exacerbations	Pre-12 m *versus* 5
	Number and rate of moderate-and-severe exacerbations	Visit 3 and 5
	Change in number and rate of moderate-and-severe exacerbations	Pre-12 m *versus* 5
	Proportion of participants withdrawn and treatment discontinued and reason	Visit 3 and 5
To assess patterns of medication use with AIR algorithm treatment	Mean ICS dose per day (budesonide μg·day^{-1})#	Visit 2 to 5
	Change in mean ICS dose per day (budesonide μg·day^{-1})	Visit 3 *versus* 5
	Mean β-agonist dose per day (formoterol μg·day^{-1})#	Visit 2 to 5
	Change in mean β-agonist dose per day (formoterol μg·day^{-1})	Visit 3 *versus* 5
	Proportion of participants requiring other asthma-related medications	Visit 3 and 5
	Longest duration of no actuations (days)#	Visit 2 to 5
	Change in longest duration of no actuations (days)	Visit 3 *versus* 5
	Proportion of days of no inhaler use#	Visit 2 to 5
	Change in proportion of days of no inhaler use	Visit 3 *versus* 5
	Number of days of high inhaler use#	Visit 2 to 5
	Change in number of days of high inhaler use	Visit 3 *versus* 5
	Number of days of marked inhaler overuse#	Visit 2 to 5
	Change in number of days of marked inhaler overuse	Visit 3 *versus* 5
	Proportion of high inhaler use episodes without medical review within 48 h	Visit 2 to 5
	Proportion of marked inhaler overuse episodes without medical review within 48 h	Visit 2 to 5
	Change in inhaler use over −7 days of treatment step up and +7 days of treatment step up	Variable
	Change in inhaler use over −7 days of treatment step up and +7 days of treatment step down	Variable

Continued

TABLE 3 Continued

Objectives	Outcome measures	Timepoint(s)
To assess the safety of AIR algorithm treatment	Adverse events	Visit 3 and 5
	Proportion with at least one related AE	Visit 3 and 5
	Serious adverse events	Visit 3 and 5
	Proportion with at least one related SAE	Visit 3 and 5
To assess participant beliefs about medicines whilst on AIR algorithm treatment	BMQ-SABA scores (Necessities and Concerns)	Visit 1, 3 and 5
	BMQ-AIR score (Necessities and Concerns)	Visit 1, 3 and 5
To assess the carbon footprint of AIR algorithm treatment	CO_2e emissions per person-year	Visit 5

AIR: Anti-Inflammatory Reliever; TSQM: Treatment Satisfaction Questionnaire for Medication; MCID: minimal clinically important difference; asthma attack: defined as a deterioration in asthma symptoms severe enough to warrant the use or prescription of systemic corticosteroids; ACQ-5: Asthma Control Questionnaire, five question (symptom-only) version; AQLQ-S: Asthma Quality of Life with Standardised Activities Questionnaire; ACT: Asthma Control Test Questionnaire; FEV_1: forced expiratory volume in 1 s; F_{ENO}: fractional exhaled nitric oxide; severe exacerbation: defined by 1) the use of systemic corticosteroids for at least 3 days because of asthma, or 2) hospitalisation or emergency department (ED) visit because of asthma, requiring systemic corticosteroids or 3) worsening asthma resulting in unplanned medical review (primary care or ED visit) severe enough to warrant an acute prescription of systemic corticosteroid; Pre-12 m: data for the 12 months prior to enrolment; moderate exacerbation: defined by 1) 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 2) worsening asthma resulting in the use of systemic corticosteroids for fewer than 3 days; ICS: inhaled corticosteroid; high inhaler use: >8 actuations of budesonide/formoterol 200/6 µg in a 24-h period; marked inhaler overuse: >12 actuations of budesonide/formoterol 200/6 µg in a 24-h period; AE: adverse event: SAE: serious adverse event; BMQ-SABA: Beliefs about Medicines Questionnaire – Short-Acting β-Agonist version; BMQ-AIR: Beliefs about Medicines Questionnaire – Anti-Inflammatory Reliever version; CO_2e: carbon dioxide-equivalent. #: outcomes will be presented 1) by AIR track treatment step at baseline and 2) by participants that have remained on the same treatment step, stepped-up or stepped-down their study treatment on entry to each visit.

framework this represents a "small" effect and may be reasonable to use to interpret the association of the TSQM and the ACQ-5.

Data collection

Data will be collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the MRINZ [31, 32]. A REDCap-based Clinical Data Management Application will facilitate the electronic collection of data in real time during clinic visits.

Statistical methods

The statistical analysis will be by intention to treat, performed by the study statistician masked as to treatment allocation. SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) will be used.

Categorical data will be summarised by counts and proportions expressed as percentages. Continuous data will be summarised by mean±$_{SD}$, 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.

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 Step at visit 1 and subsequent visits.

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

The primary analysis of the primary outcome, TSQM Global Satisfaction Score, will be by paired t-test, with associated confidence interval. The MCID for TSMQ Global Satisfaction scores will be estimated 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, to estimate the equivalent change [33, 34]. Primary analysis for estimating the MCID of the TSQM Global Satisfaction scores will use a regression approach to score 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. A regression

TABLE 4 Schedule of trial procedures

Visit number	Consent and enrolment	Visit number					
		1	2	3	4	5	Unscheduled visits
Week	⩽1	1	13	26	39	52	A/R
Day	⩽1	1	91	182	273	364	A/R
Visit window (days)	N/A	N/A	±7	±7	±7	±7	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	
F_{ENO}[¶]		X		X		X	
Spirometry		X		X		X	
Assess inhaler/reliever 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			
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
Inform GP of study enrolment		X					
Inform GP of study completion/withdrawal			A/R	A/R	A/R	X	A/R

TSQM: Treatment Satisfaction Questionnaire for Medication; ACQ-5: Asthma Control Questionnaire, five question (symptom-only) version; AQLQ-S: Asthma Quality of Life with Standardised Activities Questionnaire; ACT: Asthma Control Test Questionnaire; BMQ-SABA: Beliefs about Medicines Questionnaire – Short-Acting β-Agonist version; BMQ-AIR: Beliefs about Medicines Questionnaire – Anti-Inflammatory Reliever version; F_{ENO}: fractional exhaled nitric oxide; AEs: adverse events: SAEs: serious adverse events; GP: general practitioner; N/A: not applicable; A/R: as required. [#]: reviewed if consent and enrolment done on a different day to visit 1; [¶]: performed prior to spirometry; [+]: investigator to inform sponsor within 24 h of becoming aware of an SAE.

approach will be used to explore if *a priori* defined variables (including age, ethnicity, asthma control and history of asthma exacerbations) predict TSQM Global Satisfaction Score, adjusting for baseline score.

Differences in ACT, ACQ-5, AQLQ-S, FEV_1, F_{ENO}, ICS and β-agonist dose, and inhaler use between visits will be estimated using paired t-tests. Floor and ceiling effects with respect to ACT, ACQ-5, AQLQ-S, FEV_1 and F_{ENO} will be explored by plots to examine for nonlinearity at the extremes of scores using scatter plot smoothers, *e.g.* LOESS. F_{ENO} scores and change from baseline will be reported 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. Proportion of days of no inhaler use will be analysed by McNemar's test. Severe and moderate-and-severe exacerbations will be analysed by Poisson regression with an offset for number of days in the study. 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.

Data and safety monitoring

An independent Data and Safety Monitoring Committee (DSMC) has been established, with membership comprising clinicians with research experience. The DSMC will receive monthly reports of all adverse events, and if a safety review is deemed necessary, then termination of the trial will be considered.

Discussion

This is the first study of the AIR treatment track, a practical stepwise approach to asthma management that incorporates ICS-formoterol reliever therapy, with or without ICS-formoterol maintenance therapy, based solely on the combination budesonide–formoterol 200/6 µg DPI as recommended in the New Zealand adolescent and adult asthma guidelines published in 2020 [8]. At the time of their publication, Symbicort Turbuhaler was the only ICS–formoterol preparation approved and available for use in New Zealand as reliever therapy alone and in combination with ICS–formoterol maintenance therapy. Eligible participants will be recruited, categorised and allocated the appropriate AIR treatment track step using the GINA 2018 track criteria, as this was the last GINA recommended stepwise approach to include SABA monotherapy [7].

This study aims to establish participant satisfaction with the AIR therapy stepwise approach to the pharmacological treatment of adult asthma. Participant satisfaction was chosen for the primary outcome as this novel approach encourages patients to manage their own asthma treatment and relies on participants' willingness to engage. Participant satisfaction is an important measure in asthma management and provides a composite assessment of the acceptability of the AIR algorithm, with patient satisfaction shown to be associated with higher levels of treatment adherence and improved asthma control [35].

The TSQM was chosen as a validated and generalisable measure of the major elements of patient satisfaction with medication in chronic disease. The TSQM has been used in numerous studies for assessing satisfaction with inhaled medications and included participants with asthma in its original validation process [36–39]. The questions were deemed easy to understand, insightful and perform reliably when used with heterogeneous samples. The Global Satisfaction domain of the TSQM was chosen as the primary outcome as it is the most predictive indicator of patient satisfaction, offering a balanced judgement across all other domains (side-effects, effectiveness, convenience), whilst also accounting for participant's own unique set of values. Global Satisfaction scores were also a better predictor of adherence and likelihood of continuing on medications, deemed crucial to the assessment of patient engagement with the AIR approach going forward [19].

Whilst higher TSQM scores are indicative of increased treatment satisfaction, an MCID has not yet been established for this questionnaire in asthma patients. The MCID of the Global Satisfaction domain of the TSQM will be calculated at week 26, with a regression approach to domain scores against participant ACQ-5 scores, which could then be used to further inform the Global Satisfaction domain at week 52. A measure of asthma control was deemed most suitable for calculating the primary outcome MCID, as the modelling for Global Satisfaction correlated best with Effectiveness (path coefficient of 0.96) [19]. Of the various measures of asthma control assessed during the study, the ACQ-5 is purely symptom based and least likely to be affected by factors intrinsically linked to the AIR algorithm (*i.e.* such as reliever use).

This study will also investigate the utility of the novel AIR algorithm. Participants requiring on average two or fewer relief actuations per week are assumed to have achieved a good level of control and are therefore advised to reduce their treatment by one step, though not beyond Step 1. For participants requiring their reliever on average between two and seven actuations per week, no change is advised to current treatment step. If a participant has an asthma attack, or is taking more than seven relief actuations per week, they will be advised to increase their treatment step. This instruction is based on the knowledge that both high β_2-agonist use and a recent asthma attack are markers of poor asthma control and exacerbation risk [40, 41].

To better assess the AIR algorithm the study has been divided into two phases. In Phase 1, the AIR algorithm and associated action plan will be implemented through doctor-run clinic visits, with transition between steps calculated and implemented by study investigators, mirroring the paternalistic model of doctor–patient relationships [42]. In Phase 2, participants will be encouraged to take a more active role in their management and transition between steps themselves, without the requirement to seek clinical review prior to the treatment step decisions. This will enable patient-led asthma management, whilst ensuring symptom-driven ICS delivery that mitigates the risks introduced by potential SABA monotherapy in patients with poor maintenance ICS adherence [43].

The study will also provide a comprehensive assessment of the efficacy and safety of the AIR algorithm, as well as describe participant engagement with this novel regimen. Assessing patients' beliefs about the

specific regimen components will also provide further insights into potentially modifiable determinants of treatment engagement. This study will evaluate how patients move between steps in response to reliever use and asthma attacks, and what effect this might have on levels of asthma control, quality of life, lung function and F_{ENO} as a measure of airways inflammation.

Through the use of electronic monitoring, it will be possible to determine patterns of actual medication use and how these relate to transitioning between steps. It will also enable an assessment of safety in terms of both corticosteroid exposure and reliever overuse in the situation of worsening asthma. Given proposals that switching from inhalers with a high global warming potential, such as pressurised metered dose inhalers, to alternatives with a lower global warming potential, such as DPIs, may help reduce healthcare-associated carbon emissions, the carbon footprint ascribed to the AIR approach will also be assessed [44].

To put this study into its historical perspective, although stepwise algorithms have been recommended in international asthma guidelines for at least 30 years [1], there have been no interventional studies that have critically investigated their efficacy, safety or practical operational issues to inform their use in clinical practice. This study will address this deficiency and provide detailed information of the AIR stepwise treatment track and algorithm and a much needed knowledge base for the use of this approach in clinical practice. Specifically, this will include a multidimensional assessment of patient satisfaction, transition between steps and the impact this may have on efficacy and safety outcomes, patterns of medication use, airway anti-inflammatory activity and carbon footprint. This assessment will be made during an initial 6-month period in which changes in treatment step in accordance with the algorithm will be made by the clinician, and then a further 6-month period in which the participant self-adjusts their treatment step. We hope that this study will provide a template for the similar investigation of the use of the SABA reliever therapy-based track.

Provenance: Submitted article, peer reviewed.

This study is registered at www.anzctr.org.au with identifier number ACTRN12620001010987. Individual participant data for this trial (including data dictionaries) will be made available, upon request, 1 year after publication until a minimum of 5 years after publication. Researchers must provide a methodologically sound proposal for consideration by the AIR algorithm steering committee.

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