# Treatable traits for the management of asthma: a feasibility study

# Short title: Treatable traits feasibility

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**Confidentiality Statement**

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# 3 SYNOPSIS

| | | |
|---|---|---|
| Trial Title | Treatable traits for the management of asthma: a feasibility study | |
| Internal ref. no. (or short title) | Treatable traits feasibility (MRINZ/19/06) | |
| Clinical Phase | IIIB | |
| Trial Design | Single group cohort study | |
| Trial Participants | Participants with doctor diagnosed asthma, a history of severe exacerbation in the last year, and who are not well-controlled despite receiving treatment at Step 2 or above, do not meet the ATS/ERS definition of severe asthma, and are not currently under the care of a severe asthma clinic | |
| Planned Sample Size | 50 participants | |
| Treatment duration | 10 weeks | |
| Follow up duration | Nil | |
| Planned Trial Period | 7 Months | |
| | Objectives | Outcome Measures |
| Objectives | Estimation of recruitment rates. | Detailed screening log |
| | Estimation of the proportion who find the intervention acceptable. | Likert scale administered through end of study questionnaire |
| | Estimation of the proportion of participants would be willing to be randomised in a trial comparing guideline directed care with management according to a treatable trait based management algorithm. | Likert scale administered through end of study questionnaire |
| | Estimation of the proportion of participants requiring the extended assessment protocol at visit 3. | Proportion of participants with either an ACQ ≥ 1 at V3 or severe exacerbation between V1 and V3 |
| | Estimation of the prevalence of the traits identified during the extended assessment | Result of extended trait assessment |

# 4 ABBREVIATIONS

| | |
|---|---|
| ACQ | Asthma control questionnaire |
| AE | Adverse event |
| AR | Adverse reaction |
| AQLQ | Asthma related Quality of life Questionnaire |
| CARM | Centre for Adverse Reactions Monitoring |
| eCRF | Electronic Case Report Form |
| CT | Clinical Trials |
| CTA | Clinical Trials Authorisation |
| CTRG | Clinical Trials and Research Governance |
| DMC/DMSC | Data Monitoring Committee / Data Monitoring and Safety Committee |
| DSUR | Development Safety Update Report |
| FeNO | Fractional exhaled Nitric Oxide |
| $FEV_1$ | Forced Expiratory Volume at 1 second |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HDEC | Health and Disability Ethics Committee |
| IB | Investigators Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ICS | Inhaled corticosteroids |
| IRB | Independent Review Board |
| LABA | Long Acting Beta-Agonist |
| MRINZ | Medical Research Institute of New Zealand |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| SGRQ | St George's Respiratory Questionnaire |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |

# 5 INTRODUCTION

Asthma affects 1 in 9 adults and 1 in 7 children in New Zealand.(1) Although asthma outcomes have improved during the 1990's and 2000's there has been little improvement over the last decade and more than one person a week still dies from asthma in New Zealand. Costs to New Zealand are approximately $500 million per year.(1) As a result we need to develop new ways to manage asthma that can address the heterogeneity of asthma in the real world and incorporate advances in knowledge.(2)

The concept of treatable traits in airways disease has developed over the last decade in response to the recognition that chronic airways disease such as asthma and chronic obstructive pulmonary disease (COPD) are complex syndromes which require individualised investigation and treatment.(3–5) Underlying the diagnostic label of both are different patterns of inflammation and multiple overlapping conditions and co-morbidities. These characteristics represent treatable traits if they can be identified by clinical, biomarker, physiological or other investigations, are amenable to specific treatments, and have clinical relevance.

Investigation and treatment of 'treatable traits' in airways disease thereby provides a way in which precision medicine can be practised for individual patients. The aim being to improve clinical outcomes for individual patients by targeting specific treatments to optimize efficacy, while minimizing unnecessary side-effects for those less likely to respond to given treatments.(6)

Some aspects of this approach are widely used internationally in tertiary hospital severe asthma clinics, under the label of systematic or multidimensional assessment, and this is associated with improvements in asthma control and quality of life and a reduction in severe exacerbations.(7) However: *1)* there is very limited RCT evidence for the treatable traits approach in the management of asthma and its efficacy in people with less severe asthma; and, *2)* it is unclear if this strategy can be applied outside tertiary referral clinics.

A full randomised controlled trial is required to determine whether treatable trait based protocolised asthma management strategies are superior to guideline directed care in people with moderate and severe asthma. This feasibility study aims to determine whether the planned full randomised controlled trial is feasible with the current design and timescale.

The algorithmic adjustment of inhaled corticosteroids and bronchodilators used in this study is different to ones tested in previous studies which used FeNO or induced sputum measurements to guide escalation of treatment.(8, 9) This is because a program of studies using as-needed Symbicort (10–12) has clearly shown that as-needed budesonide-formoterol is superior to PRN salbutamol or terbutaline for asthma control and exacerbation risk. Accordingly the Global Initiative for Asthma (GINA) have listed as-needed ICS-formoterol as the preferred reliever for all patients with asthma in the GINA strategy framework, either as as-needed therapy in mild asthma or maintenance and reliever therapy in moderate to severe asthma. With anti-inflammatory reliever therapy now recommended for all patients with asthma the current study management algorithm is built on an anti-inflammatory reliever backbone. Potentially steroid responsive airway inflammation is assessed using FeNO and blood eosinophils and anti-inflammatory treatment escalated as required. Airflow obstruction is assessed using spirometry and bronchodilator therapy escalated if airflow obstruction is present.

# 6 OBJECTIVES

There are five specific feasibility issues which will be addressed to determine whether any changes need to be made to the design of the full study prior to it being conducted:

| **Objectives** | **Outcome Measures** |
|---|---|
| 1) Estimation of recruitment rates. | Detailed screening log |
| 2) Estimation of the proportion who find the intervention acceptable. | Likert scale administered through end of study questionnaire |
| 3) Estimation of the proportion of participants who would be willing to be randomised in a trial comparing guideline directed care with management according to a treatable traits based management algorithm. | Likert scale administered through end of study questionnaire |
| 4) Estimation of the proportion of participants requiring the extended assessment protocol at visit 3. | Proportion of participants with either an ACQ ≥ 1 at V3 or exacerbation between V1 and V3 |
| 5) Estimation of the prevalence of the traits identified during the extended assessment | Proportion of participants in whom each trait is deemed to be present according to the assessment algorithm. |

# 7 TRIAL DESIGN

This is a single group cohort study with 50 participants. Participants will be recruited from the community, through tertiary and primary care using research databases of the centres and through media. Study visits will be conducted at 2 sites: Newcastle, Australia; and Wellington, NZ. Participants will attend an initial screening visit to determine eligibility. If eligible, each participant will be enrolled and have 2 further visits over a 10 week period. Each visit will last up to 2 hours each. A summary of procedures that will be undertaken during all visits is presented in Table 1.

## 7.1 PARTICIPANT IDENTIFICATION

Potential participants with a doctor's diagnosis of asthma will be identified from existing research institute databases, asthma clinicians, GP mailouts and direct advertising (including via social media). Potential participants who have given permission to be contacted about upcoming research projects will be contacted via telephone or email by a study investigator. If interested, participants will be sent out a Participant Information Sheet. Once an appropriate amount of time has been given for the potential participant to consider the information, they will be contacted again by a study investigator to discuss attending an initial screening visit. Potential participants will be encouraged to discuss the PIS and their involvement in the study with family, whānau (NZ), and their healthcare provider.

### 7.1.1 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Aged 18 to 75 years on day of enrolment.
- Self-report of a doctor's diagnosis of asthma.
- Asthma not well-controlled, as measured by an ACQ score ≥1.
- Severe asthma exacerbation within the previous year as defined in Section 10.1
- Receiving treatment with an inhaled corticosteroid containing medication for at least 3 months
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
- Willing to allow his or her General Practitioner and consultant, where relevant, to be notified of participation in the trial.

### 7.1.2 Exclusion Criteria

- Inhaled corticosteroid dose >1000mcg fluticasone propionate (FP)/day or equivalent.
- Maintenance oral corticosteroid use for any indication (regular hydrocortisone or fludrocortisone are permitted).
- Oral corticosteroid use within the previous 4 weeks for any indication (regular hydrocortisone or fludrocortisone are permitted).
- Under the care of a severe asthma clinic
- Anti-IgE or anti-IL5 biologics within the previous 4 weeks
- Current immune suppression or immunodeficiency
- Previous ICU admission due to asthma
- Participant who is pregnant, lactating, or planning pregnancy during the course of the trial.

- Serious co-morbidity liable to affect ability to perform study procedures or interpretation of study results, e.g. recent pneumothorax, interstitial lung disease, bronchiectasis, severe heart failure, myocardial infarction within the last 3 months.
- Any other significant disease or disorder (including known contraindication to any of the IMPs or excipients) that, in the opinion of the Investigator, may put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
- Participants who have participated in another research trial involving an investigational product in the past 12 weeks.

# 8 TRIAL PROCEDURES

The trial schematic and individual visit workflow are shown in Figure 1. The schedule of procedures is shown in Table 1 and individual study procedures are described below.

**Table 1: Schedule of Study Procedures**

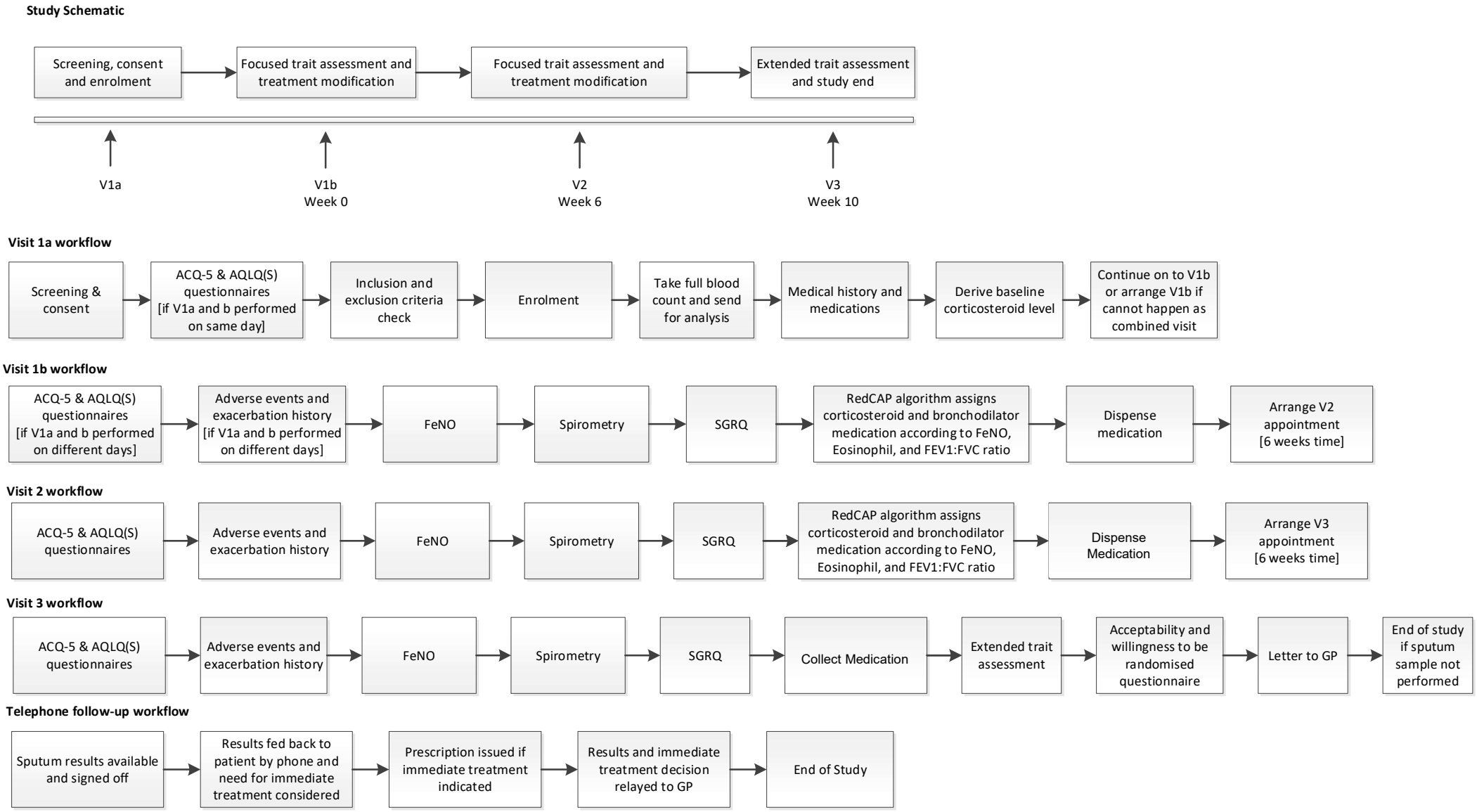
| Visit Number | 1a | 1b | 2 | 3 | Telephone follow-up |
|---|---|---|---|---|---|
| Week | 0 | 0 | 6 | 10 | 11 |
| Day | 0 | 0 | 42 | 70 | 77 |
| Visit Window (Days) | n/a | +7 | ±7 | ±7 | ±3 |
| Written informed consent | X | | | | |
| Urinary pregnancy test[€] | X | | | | |
| Inclusion/Exclusion criteria check | X | | | | |
| Enrolment | X | | | | |
| Inform GP of study enrolment | | X | | | |
| ACQ-5 | X[¥] | X* | X | X | |
| AQLQ(S) Questionnaire | X[¥] | X* | X | X | |
| Blood test for full blood count and CRP | X | | X[#] | X[#] | |
| Review of exacerbations, AEs/SAEs, and con-meds | | X* | X | X | |
| St George's Respiratory Questionnaire (SGRQ) | | X | X | X | |
| Medical history & demographics | | X | | | |
| Weight and height | | X | | | |
| Self-reported smoking status | | X | X | X | |
| Exhaled carbon monoxide / urinary cotinine | | X | X | X | |
| FeNO[$] | | X | X | X | |
| Pre-bronchodilator spirometry | | X | | | |
| Reversibility to salbutamol | | X | | | |
| On-treatment spirometry | | | X | X | |
| Protocolised alteration of study medication | | X | X | | |
| Inhaler Technique check and education | | X | X | X | |
| Focused treatable traits assessment medication assignment (Type 2 status and Airflow limitation) | | X | X | | |
| Provide Asthma Action Management Plan | | X | X | X | |
| Dispensing of study inhalers | | X | X | | |
| Extended treatable traits assessment | | | | X | |
| Review of identified traits | | | | X | |
| End of Study Questionnaire | | | | X | |
| If participant is to be withdrawn, documentation of cause and notification to GP and Sponsor | | | X | X | |
| Inform GP and Sponsor of participant study completion | | | | X | |
| Follow-up results of sputum culture if sent (including informing the participant and participant's GP of results) | | | | | X |

*Only performed if consent and enrolment done on a different day to Visit 1b.

[¥]If consent and enrolment done on the same day as Visit 1b.

[€]Only in people who are potentially able to bear children [$]Performed prior to spirometry. [#] Blood can be taken up to 24 hours prior to Visit 2 and 3 so that the results are available at the time of the visit.

## Figure 1: Study schematic and individual visit workflow



## 8.1 INFORMED CONSENT

The participant must personally complete the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: why the trial is being conducted, procedures to be performed by participants, total duration of the study, participant benefits of being involved; 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 wished 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. After adequate time has been given, all queries have been addressed and the clinical research team is confident that the patient understands the study and all of its requirements, participants will provide written, informed consent to participate. Written Informed Consent (including e-consent where used) will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. If e-consent is utilised, an e-signature is deemed to be the equivalent of a wet ink signature. The person who obtained the consent should determine that the patient is fully informed of the study in accordance with International Conference on Harmonisation Good Clinical Practice guidelines. Consent will be taken by a member of the study team who is trained in Good Clinical Practice and who has been delegated by the Principal Investigator to undertake this activity. Patients will be consented prior to any study-related activities being undertaken. A copy of the signed Informed Consent will be given to the participant. The original signature will be retained at the local site.

## 8.2 CULTURAL SAFETY

Aboriginal and Torres Strait Islander Peoples may be incidentally recruited into this study. If a participant identifies as Aboriginal or Torres Strait Islander in the demographics questionnaire during the baseline assessment, the research officer will ask the participant if they would like to reschedule their assessment so that an Aboriginal and Torres Strait Islander liaison officer may attend with them. The study protocol is consistent with the 2018 guidance "Ethical conduct in research with Aboriginal and Torres Strait Islander Peoples and communities: Guidelines for researchers and stakeholders". It upholds the core values of spirit and integrity; cultural continuity; equity; reciprocity; respect; and responsibility.

Māori participants are likely to be recruited in New Zealand. When providing information, answering questions and taking consent every effort will be made to ensure the concept of Manaakitanga is upheld by addressing cultural sensitivity, cultural safety and Māhaki (respectful conduct), as per the 'HRC Guidelines for Researchers involving Māori', (Version 2). We will follow the Tikanga Māori Capital and Coast District Health Board Guidelines. We will provide time for any cultural issues associated with blood tests to be discussed with family/whānau as appropriate, and participants will be able to access support from Whānau care services if they would like. The informed consent process will also involve discussion of these issues with a study investigator. It is also recognised that there are a range of views held by Māori around these issues. We acknowledge that individuals have the right to choose to not have the blood tests, but this will require exclusion from the study. Any

New Zealand based research staff carrying out duties as part of this study will arrange Tikanga-Māori Research Specific education, if they have not done so already.

## 8.3 SCREENING AND ELIGIBILITY ASSESSMENT

Potential participants will attend the research facility for a screening visit (V1a) at which the PIS will be discussed and written informed consent will be completed. At this visit eligibility will be assessed. If a potential participant is deemed ineligible, then a reason for this will be recorded. Participant's GPs will be notified regarding their enrolment in the study.

## 8.4 ACQ-5 & AQLQ(S)

### 8.4.1 Asthma Control Questionnaire, five question version (ACQ-5)

ACQ-5 will be administered prior to history taking or spirometry. The questionnaire will be in a paper format. The participant should read and fill it in without intervention by the investigator. Where this is not possible the investigator may read and/or record answers for them, however it must be documented that this took place.

### 8.4.2 Asthma Quality of Life Questionnaire, standardised version, AQLQ(S)

The questionnaire will be in a paper format. The participant should read and fill it in without intervention by the investigator. Where this is not possible the investigator may read and/or record answers for them, however it must be documented that this took place.

## 8.5 LABORATORY TESTING

Venous blood will be drawn into one EDTA tube and one SST tube (or appropriate local equivalent) for analysis of full blood count and C-reactive protein in line with the site's standard operating procedures. Samples will be analysed at the local accredited laboratory which must provide blood eosinophil count ($x10^{-9}$/L) to two decimal places.

## 8.6 MEDICAL HISTORY AND DEMOGRAPHICS

The information collected will include the following:

- Date of birth, age, ethnicity, sex.
- Height and weight
- Participant contact details and emergency contact details
- GPs contact details
- Smoking history: smoking status (ex, current, never), pack years
- Age at asthma diagnosis
- Asthma history including whether ever hospitalised for asthma, ever been to ED for asthma, history of exacerbations and need for oral steroids to treat uncontrolled asthma in the previous year and date of most recent exacerbation
- Cardiovascular history
- Current medications for asthma
- Other medical conditions and medications
- Allergies

- Pregnancy status (where appropriate)
- Inhaler technique at study entry
- Use of asthma self-management plan at study entry

## 8.7 VISIT 1B

Visit 1b can be combined with visit 1. However, if the blood eosinophil count result is not expected to be available by the end of V1b then V1b can be deferred by up to 7 days to ensure that the blood eosinophil count is available for protocolised treatment adjustment.

## 8.8 ST GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

The questionnaire will be in a paper format. The participant should read and fill it in without intervention by the investigator. Where this is not possible the investigator may read and/or record answers for them, however it must be documented that this took place.

## 8.9 FENO

FeNO will be measured on NiOX Vero, made by Circassia in Sweden in accordance with guidelines published by the ATS 2005(13). FeNO will be measured prior to spirometry at each visit. Participants will be asked not to consume food or caffeinated beverages for at least 1 hour prior to their FeNO measurement. Participants will be advised to avoid consumption of nitrate-rich foods (such as processed meats [bacon, lunch meat, hot dogs, sausage etc.], spinach, green beans, broccoli, and cauliflower) for at least 8 hours prior to FeNO measurement. FeNO must be collected prior to spirometry. The mean of 3 repeatable measurements is taken. For a measurement to be deemed repeatable all accepted measurements should be within 10% of the mean. If 3 repeatable measurements cannot be obtained the mean of 2 repeatable measurements can be used.

## 8.10 PRE-BRONCHODILATOR SPIROMETRY AND REVERSIBILITY TO SALBUTAMOL

Spirometry, including FEV1 and forced vital capacity (FVC), will be performed in accordance with the guidelines outlined by the American Thoracic Society(14) using a hand-held spirometer.

### 8.10.1 Bronchodilator reversibility

This will be performed in all participants in accordance with ATS/ERS guidelines.

The MDI will be shaken, placed into the end of the spacer and fired once. The participant will then:

1) Exhale to FRC
2) Place lips around volumatic and inhale deeply and slowly
3) Hold breath for 10 – 15 seconds
4) Exhale

The inhaler is fired again and steps 1- 4 should be repeated. If the participant cannot perform a 10 second breath hold then steps 2 & 3 can be replaced by tidal breathing for 6 breaths.

Post-bronchodilator pulmonary function tests will be performed between 10 and 15 minutes after the administration of the bronchodilator.

## 8.11 PREGNANCY TESTING

A urinary pregnancy test will be carried out at visit 1b for participants in whom that is appropriate.

## 8.12 SMOKING STATUS

A participant is defined as a 'current smoker' if they self-report smoking any tobacco product, either daily or occasionally, within the last 28 days or they have a positive urinary cotinine or exhaled carbon monoxide test during that visit.

'Ex-smoker' is someone who has smoked greater than 100 cigarettes (including hand rolled cigarettes, cigars, cigarillos etc) in their lifetime but has not smoked in the last 28 days and has a negative urinary cotinine or exhaled carbon monoxide test during that visit.

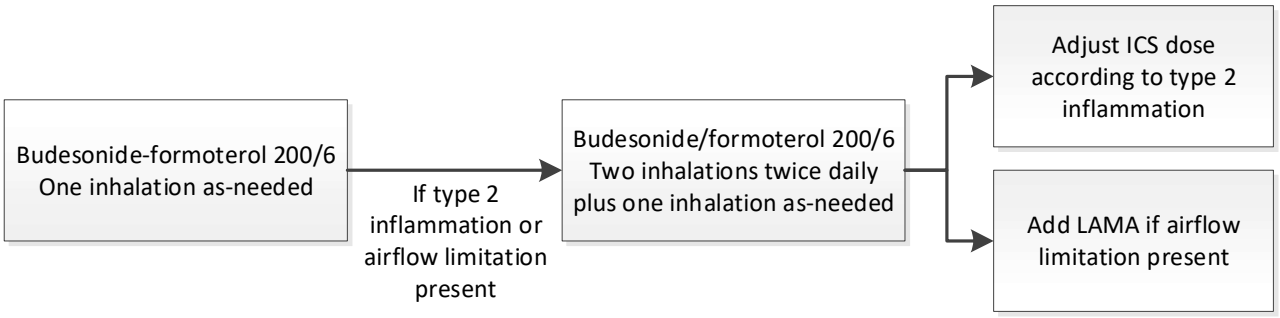
'Never-smoker' is someone who has smoked fewer than 100 cigarettes (including hand rolled cigarettes, cigars, cigarillos etc) in their lifetime and has not smoked in the last 28 days and has a negative urinary cotinine or exhaled carbon monoxide test during that visit.

Cotinine testing at each visit to confirm status as a non-smoker.

## 8.13 FOCUSED TREATABLE TRAITS ASSESSMENT

Anti-inflammatory reliever therapy is the preferred reliever in the 2019 GINA strategy framework.(15) The focused treatable traits approach will use measurement of Type 2 inflammation and airflow limitation to guide treatment escalation within an anti-inflammatory reliever paradigm (Figure 2).

**Figure 2: Focused treatable traits treatment escalation**




At visit 1a the participant's baseline corticosteroid treatment level will be determined (Table 2).

The presence of Type 2 airway inflammation is inferred based on blood eosinophil count and FeNO (Table 3 and 5). At Visits 1b & 2 the traits of Type 2 airway inflammation and airflow limitation will be assessed and inhaled medication will be adjusted according to the Type 2 inflammation and airflow limitation management algorithms below (Tables 4,5 & 6).

All participants will receive a minimum of budesonide/formoterol 200/6 Turbuhaler one inhalation as required as a reliever,(10, 11, 16) irrespective of baseline inflammatory status.

The presence of airflow limitation is determined by a pre-bronchodilator (V1b) or on treatment (V2 and V3) FEV1:FVC ratio below the lower limit of normal for that individual (Table 6). A fixed 0.7 cut-off is not used because this underestimates the presence of airflow limitation in younger patients. The presence of airflow limitation on pre-bronchodilator spirometry indicates a requirement for regular long-acting bronchodilator. If the participant is not already on a regular long-acting beta-agonist then one will be started by initiating Symbicort as maintenance and reliever therapy (SMART). If already on SMART then regular long-acting muscarinic antagonist will be added, in the form of tiotropium

Respimat 2.5mcg two inhalations once daily.

Once the assessment has been completed, a participant's medication for that treatment period is then assigned by the algorithm. The assigned medication will be dispensed and an accompanying Asthma Action Management Plan will be provided to and reviewed by the participant. The management plan will specify the medications, including dose and frequency, that have been assigned based on the algorithm. The management plan will also give advice in the event of an exacerbation.

## 8.14 EXAMPLE PARTICIPANT

The participant consents to take part in the study, meets the inclusion and exclusion criteria, and is enrolled. Their baseline inhaled medication is flixotide 100mcg two inhalations twice daily, total 400mcg daily. Their baseline corticosteroid level according to Table 2 would be Level 2.

Their initial focused assessment demonstrates FeNO 70ppb, Blood Eos $0.4x10^9$. This would be interpreted as strong evidence of Type 2 inflammation [see Table 5] meaning that corticosteroid treatment should be increased to Level 3. Spirometry shows an FEV1:FVC ratio of 85% and therefore the airflow limitation trait is not present.

Treatment assignment at V1b:

- Type 2 inflammation trait: Level 3 treatment (Budesonide/formoterol 200/6 Turbuhaler Two inhalations twice daily and one inhalation as-needed)
- Airflow limitation trait: Airflow limitation not present so no additional regular bronchodilator above that already given as a result of the Type 2 inflammation algorithm.

At visit 2 the assessment finds:

- FeNO 30ppb
- Blood eos. $0.2x10^9$
- ACQ 0.3
- FEV1:FVC ratio >LLN

Treatment assignment at V2:

- Type 2 inflammation trait: No change to current treatment as intermediate evidence of T2 inflammation and asthma well-controlled (ACQ < 1) [see Table 5]
- Airflow limitation trait: No change to current treatment [see Table 6]

At visit 3 the assessment finds:

- FeNO 15ppb
- Blood eos. $0.2x10^9$
- ACQ 0.3
- FEV1:FVC ratio >LLN
- Extended assessment finds evidence of rhinosinusitis

The participant is informed that in a full RCT they would be continued on the same inhaled treatment but also dispensed nasal corticosteroids for their rhinosinusitis. They are then asked to complete the end of study questionnaire (appendix 2). No further treatment adjustment takes place and their involvement in the study is complete.

The investigator provides a summary letter for the participant's usual medical provider and agrees an interim treatment plan pending further review, issuing a prescription if required.

**Table 2: Study entry corticosteroid dosing equivalence**

| Pre-study | Study starting level |
|---|---|
| Fluticasone propionate 250mcg daily or below<br>Budesonide 400mcg daily or below<br>Beclomethasone 500mcg daily or below | Level 1 |
| Fluticasone propionate >250mcg and up to 500mcg daily<br>Budesonide >400mcg and up to 800mcg daily<br>Beclomethasone >500mcg and up to 1000mcg daily<br>Fluticasone furoate 100mcg daily | Level 2 |
| Fluticasone propionate >500mcg and up to 1000mcg daily<br>Budesonide >800mcg and up to 1600mcg daily<br>Beclomethasone >1000mcg and up to 2000mcg daily | Level 3 |

**Table 3: Biomarker cut-points:**

| | Blood Eosinophils (x$10^9$) | FeNO (ppb) | |
|---|---|---|---|
| | | Non-smoker | Current smoker |
| High | ≥0.3 | ≥40 | ≥28 |
| Intermediate | ≥0.15 and <0.3 | ≥ 20 and <40 | ≥ 14 and <28 |
| Low | <0.15 | <20 | <14 |

**Table 4: Type 2 inflammation trait- Corticosteroid treatment levels**

| Level | | Daily FP dose equivalent |
|---|---|---|
| 1 | No regular ICS | 0mcg |
| | Budesonide/formoterol 200/6 Turbuhaler one inhalation as needed | |
| 2 | Budesonide/formoterol 200/6 Turbuhaler Two inhalations twice daily and one as-needed | At least 500 mcg (exact dose dependent on as needed use) |
| 3 | Budesonide/formoterol 200/6 Turbuhaler Two inhalations twice daily and one as-needed *plus* | At least 1000 mcg (exact dose dependent on as needed use) |
| | Budesonide 200mcg Turbuhaler Two inhalations twice daily | |
| 4 | Budesonide/formoterol 200/6 Turbuhaler Two inhalations twice daily and one as-needed *plus* | At least 1000 mcg (exact dose dependent on as needed use) plus oral steroid |
| | Budesonide 200mcg Turbuhaler Two inhalations twice daily *plus* | |
| | Oral prednisone 10mg daily | |
| 5 | Budesonide/formoterol 200/6 Turbuhaler Two inhalations twice daily and one as-needed *plus* | At least 1000 mcg (exact dose dependent on as needed use) plus oral steroid |
| | Budesonide 200mcg Turbuhaler Two inhalations twice daily *plus* | |
| | Oral prednisone 20mg daily | |

**Table 5: Type 2 inflammation trait: Corticosteroid dosing adjustment algorithm**

| Biomarker results | Asthma control | Interpretation | Treatment change |
|---|---|---|---|
| Either FeNO or blood Eos or both are high | ACQ score ≥ 1 | Strong evidence of T2 inflammation and not well controlled asthma (ACQ ≥ 1) | Increase corticosteroid treatment by one level. |
| Either FeNO or blood Eos or both are high | ACQ score <1 | Strong evidence of T2 inflammation and well controlled asthma (ACQ < 1) | Increase corticosteroid treatment by one level up until to level 3. Do not escalate above level 3.* |
| At least one of FeNO and blood Eos are in the intermediate range and neither are high | ACQ ≥ 1 | Intermediate evidence of T2 inflammation and not well-controlled asthma (ACQ ≥ 1) | Increase corticosteroid treatment by one level |
| At least one of FeNO and blood Eos are in the intermediate range and neither are high | ACQ < 1 | Intermediate evidence of T2 inflammation and well controlled asthma (ACQ < 1) | No change to corticosteroid treatment |
| Both FeNO and blood EOS are low | Any ACQ score | No evidence of T2 inflammation | No change to corticosteroid treatment |

As the study is only 10 weeks long there will be no reduction in corticosteroid treatment during the study. A future full-scale RCT would include the option of reducing corticosteroid treatment by one level if the participant had had no evidence of T2 inflammation on two occasions over a 3 month period. *Only patients who do not have well-controlled asthma will receive oral corticosteroids due to the risks associated with oral corticosteroids.

**Table 6: Airflow limitation trait: bronchodilator algorithm**

| Pre-bronchodilator / on-treatment FEV1:FVC ratio | Treatment change |
|---|---|
| ≥ LLN | No change to bronchodilator treatment |
| < LLN | **If not on regular LABA:** Start regular long-acting beta-agonist by stepping up from as-needed to maintenance and reliever therapy<br>**If on regular LABA:** Add Tiotropium Respimat 2.5µg two inhalations once daily in addition to treatment as per Type 2 algorithm |

As the study is only 10 weeks long there will be no reduction in bronchodilator treatment during the study. A future full-scale RCT would include the option of stopping tiotropium if the participant had had no evidence of airflow limitation on two occasions over a 3 month period and no exacerbations during that time.

**Table 7: Dispensed medication- all possible combinations**

**A) Not currently on regular LABA**

| T2 trait medication level | Airflow limitation trait present | Dispensed medication |
|---|---|---|
| 1 | No | Budesonide/formoterol 200/6<br>One inhalation as needed |
| 1 | Yes | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed |
| 2 | No | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed |
| 2 | Yes | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed |

**B) Currently on regular LABA**

| T2 trait medication level | Airflow limitation trait present | Dispensed medication |
|---|---|---|
| 2 | No | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed |
| 2 | Yes | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed<br>Plus Tiotropium Respimat 2.5mcg two inhalations once daily |
| 3 | No | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed<br>Plus Budesonide 200mcg two inhalations twice daily |
| 3 | Yes | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed<br>Plus Budesonide 200mcg two inhalations twice daily<br>Plus Tiotropium Respimat 2.5mcg two inhalations once daily |
| 4 | No | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed<br>Plus Budesonide 200mcg two inhalations twice daily<br>Plus Prednisone 10mg daily |
| 4 | Yes | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed<br>Plus Budesonide 200mcg two inhalations twice daily<br>Plus Tiotropium Respimat 2.5mcg two inhalations once daily<br>Plus Prednisone 10mg daily |
| 5 | No | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed<br>Plus Budesonide 200mcg two inhalations twice daily<br>Plus Prednisone 20mg daily |
| 5 | Yes | Budesonide/formoterol 200/6<br>Two inhalations twice daily plus one inhalation as-needed<br>Plus Budesonide 200mcg two inhalations twice daily<br>Plus Tiotropium Respimat 2.5mcg two inhalations once daily<br>Plus Prednisone 20mg daily |

## 8.15 VISIT 2

At Visit 2 participants will complete the ACQ-5 and AQLQ prior to recording of exacerbation and adverse event history.

Participants in New Zealand may have had a full blood count sample taken in the previous 24hrs. If a full blood count has not been performed in the previous 24hrs or the participant is based in Australia a full blood count sample will be drawn and sent for urgent processing. The participant will then complete FeNO measurement, spirometry and SGRQ measurement in the same manner as for Visit 1B.

Once Visit 2 ACQ-5, FeNO, spirometry and blood eosinophil count are available medication can be allocated and dispensed as described above.

## 8.16 EXTENDED TRAIT ASSESSMENT

At Visit 3 participants will undergo the same procedures as visit 2 and in addition will receive an extended assessment as per Table 8:

**Table 8: Airflow limitation trait: bronchodilator algorithm**

| Trait | Trait Identification marker |
|---|---|
| Smoking | Urinary cotinine if acceptable to patient.<br>Exhaled breath carbon monoxide if patient prefers. |
| Airway pathogen colonisation | Presence of bacterial pathogen via sputum culture |
| Frequent chest infection | ≥2 respiratory-related antibiotic courses in 12 months |
| Rhinitis / Sinusitis | Sinonasal Questionnaire score ≥1 |
| Dysfunctional breathing | Nijmegen questionnaire total score ≥23 |
| Vocal Cord Dysfunction / Inducible Laryngeal Obstruction | Pittsburg score (cut-off ≥4) and VCDQ (cut-off >40) will be collected |
| Depression &/or anxiety | HADS depression/anxiety domain score ≥8 |
| Poor adherence | <80% adherence based on number of doses administered versus expected as estimated using dose counter recordings taken at visit 2 and 3 |
| Systemic inflammation | Elevation of at least two systemic inflammatory markers on more than one occasion, high sensitivity CRP > 3mg/L, and WCC > 9 $x10^9$/ L |
| Occupational exposure | Systematic exposure hx |

## 8.17 ACCEPTABILITY AND WILLINGNESS TO BE RANDOMISED QUESTIONNAIRE

At visit 3 participants will be asked to complete a questionnaire (Appendix 2) in which they will be asked to rate the acceptability of the investigations and interventions they have undergone during the study and their willingness to have been randomised in to a full RCT comparing Usual care and treatable traits based management.

## 8.18 SUBSEQUENT VISITS

Participants who do not have a productive cough and therefore cannot provide a sputum sample as part of the extended trait assessment will not have a follow-up requirement after completion of visit 3.

Participants who do have a productive cough and provide a sputum sample for the extended trait assessment will be contacted by telephone within 1 week of Visit 3. The results of the sputum culture will be shared with them and treatment of standard respiratory pathogens initiated. The results of the sputum culture and any treatment provided will be communicated to the GP.

There will be no further routine contact with participants after the telephone follow-up. Adverse events will be followed up as described in section 9.

## 8.19 PROCEDURES FOR HANDLING INCORRECTLY ENROLLED PARTICIPANTS

Participants who fail to meet the eligibility criteria should not, under any circumstances be enrolled. There can be no exceptions to this rule. Participants who are enrolled, but subsequently found not to meet all the eligibility criteria should be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is enrolled in error, the Investigator should inform the Sponsor immediately. The Sponsor must ensure all decisions are appropriately documented.

## 8.20 Discontinuation/Withdrawal of Participants from Trial

Each participant has the right to withdraw from the trial at any time. A participant that decides to discontinue will always be asked about the reason(s) and the presence of any adverse events but the right of the patient to refuse to participate in the study without giving reasons will be respected. In addition, the Investigator may discontinue a participant from the trial treatments at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (participant enrolled in error)
- Significant protocol deviation
- Significant 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
- Requirement for medications that would make a participant ineligible as listed in Section 9.5
- Withdrawal of Consent

Participants who withdraw will not be replaced. The reason for withdrawal if given by the participant will be recorded in the eCRF. If withdrawal from or discontinuation of the study is due to an adverse event, the Investigator will arrange follow-up visits and/or telephone calls until the adverse event has resolved or stabilised. It is the intent that participants attend their scheduled follow-up visits regardless of treatment withdrawal and the participant will be encouraged to continue to participate in this follow-up, however it is recognised that this is not mandated after withdrawal of consent. The data of all eligible participants will be included in the data analysis unless the participant withdraws their consent to do so or they have been found to be incorrectly enrolled.

## 8.21 Definition of End of Trial

The end of the trial is the date and time of completion of the last visit, telephone or in person, by the final participant.

## 8.22 Concomitant Medication

All concomitant medications are permissible during the study unless they lead to a participant fulfilling an exclusion criterion.

## 8.23 Post-trial Treatment

There will be no post-trial treatment or provision of the IMP beyond the trial period.

# 9 SAFETY REPORTING

## 9.1 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.<br><br>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.<br><br>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. |
| Exacerbation | An asthma exacerbation is defined by any of the following criteria:<br><br>a. Worsening asthma resulting in unplanned medical review (primary care visit, ED visit or hospital admission) and/or<br><br>b. Worsening asthma resulting in the use of systemic corticosteroids, such as a course of oral prednisone for any duration |
| Serious Adverse Event (SAE) | A serious adverse event is any untoward medical occurrence that:<br><br>results in death<br>is life-threatening<br>requires inpatient hospitalisation or prolongation of existing hospitalisation<br>results in persistent or significant disability/incapacity<br>consists of a congenital anomaly or birth defect.<br><br>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.<br><br>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:<br><br>in the case of a product with a marketing authorisation, in the datasheet or product information for that product<br>in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question. |
| Severe Exacerbation of Asthma | A severe asthma exacerbation is defined as a presentation to a general practice, after-hours clinic or emergency department resulting in a prescription for oral corticosteroids or treatment with spacer-delivered or nebulised bronchodilator, or self-administration of prednisone for asthma for at least 3 days. |

NB: 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.

As detailed in section 9.8, pregnancy occurring during the course of the study will not be considered an adverse event; however, 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".

## 9.2 CAUSALITY

The relationship of each adverse event to the trial intervention 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 probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

## 9.3 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.

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.

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

It will be left to the Investigator's clinical judgment or the Sponsor to decide whether or not an AE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from the study. 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.

## 9.4 Reporting Procedures for Serious Adverse Events

Serious Adverse Events will be recorded in the eCRF from the date of consent until the last study visit a participant attends, and reported to the Sponsor within 24 hours of Investigators becoming aware of the event. Any follow up information required by the Sponsor must be reported as soon as the Investigator becomes aware of new information. If an SAE is ongoing at the last contact visit, the Investigator should follow this up until medically indicated, but this will not require recording in the eCRF. The Sponsor will report all serious adverse reactions in accordance with current reporting requirements.

## 9.5 Expectedness

Expectedness will be determined according to the current Medsafe Data Sheet (NZ) or the Product Information (Australia) for each IMP respectively.

## 9.6 SUSAR Reporting

All SUSARs will be reported by the Sponsor to the relevant regulatory authority as per the requirements in each country. 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.

## 9.7 Pregnancy

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

## 9.8 Maternal exposure

If a participant becomes pregnant during the course of the study, they will be from the study. Pregnancy itself is not regarded as an adverse event. 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 even if the participant was discontinued from the study. If any pregnancy occurs during the course of the study, then the Investigator will inform the Sponsor

within 1 day i.e., immediately but **no later than 24 hours** from 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 within 1 or 5 calendar days for SAEs and within 30 days for all other pregnancies. SAEs will be reported to CARM if applicable. The same timelines will apply when outcome information is available.

### 9.9 PATERNAL EXPOSURE

The study does not require abstinence or use of contraception for male partners. As the investigational product is not contraindicated in pregnancy, we will not be eliciting the pregnancy status of participants' partners.

### 9.10 SAFETY MONITORING COMMITTEE

A Data Safety Monitoring Committee (DSMC) will be formed to review all SAEs on an expedited basis, and undertake a review of enrolments, withdrawals, and adverse events on a regular basis, to ensure adequate study safety and minimal risk to participants. The DSMC may recommend to the study sponsor that the study should be stopped, however the final decision will rest with the study sponsor.

# 10 STATISTICS

### 10.1 DESCRIPTION OF STATISTICAL METHODS

The statistical analysis will address the five specified feasibility issues:

1) Estimation of recruitment rates. Reported descriptively based on detailed screening logs

2) Estimation of the proportion who find the intervention acceptable. Analysed as the proportion of participants answering the acceptability question on the end of study questionnaire as "Agree" or "Strongly agree".

3) Estimation of the proportion of participants who would be willing to be randomised in a trial comparing guideline directed care with management according to a treatable traits based management algorithm. Analysed as the proportion of participants answering the future study question on the end of study questionnaire as "Agree" or "Strongly agree".

4) Estimation of the proportion of participants requiring the extended assessment protocol at visit 3. Analysed as the proportion of participants with either an ACQ ≥ 1 at V3 or exacerbation between V1 and V3.

5) Estimation of the prevalence of the traits identified during the extended assessment. Analysed as the proportion of participants in whom each trait is deemed to be present according to the assessment algorithm.

Estimates of 95% confidence intervals for proportions will be by small sample techniques e.g. the Clopper-Pearson method.

Data for FeNO will be analysed using summary description of continuous variables for log FeNO as well as FeNO based on our previous experience with the skew distribution of this variable and that normality assumptions were better met on the logarithm transformed scale..

## 10.2 The Number of Participants

The sample size calculation for the feasibility study takes into account the following considerations:

- A recruitment rate of less than 25% of those approached for participation in the main trial means either that the main trial would need to run over a longer period of time or that more centres would need to be involved for the recruitment to occur in the time period fundable by a grant.
- This recruitment rate estimation of the feasibility study is made of two components: the proportion of those approached for the feasibility study who agree to participate,[Objective 1] and the proportion of those who participate in the feasibility study that would agree to enter a randomised trial [Objective 3]. We anticipate that 50% of those approached for the feasibility study would agree to participate in the feasibility study [Objective 1], and that 80% of those who participate in the feasibility study would agree to be randomised,[Objective 3] for a potential recruitment rate of 40% of those who are approached. If this combined proportion is less than 25% the main study would need either a longer duration or more centres than we currently anticipate.
- A sample size for recruitment of 100 has about 90% power to rule out a lower confidence bound for the recruitment proportion of less than 25%. If 50 participants are recruited into the feasibility study then this gives a 95% CI for a proportion [Objectives 2,3, & 4] of plus or minus 15%, which is useful for our planning purposes for the main study.

## 10.3 Criteria for the Termination of the Trial

Early termination may occur at the discretion of the Investigators for any reason that is believed may present a safety risk.

- Sponsor: If the Sponsor terminates or suspends a trial, the Sponsor should promptly inform the responsible ethics committee and provide them with a detailed written explanation for the termination or suspension.
- Responsible Ethics Committee: If the ethics committee terminates or suspends its approval/favourable opinion of a trial, the Sponsor will provide a detailed written explanation for the termination or suspension to all relevant parties, including but not limited to the DSMC and all Principal Investigators.

## 10.4 Procedure for Accounting for Missing, Unused and Spurious Data

The main analysis uses all available data and no form of imputation will be used for missing data. Missing at random will be assumed.

### 10.5 Inclusion in Analysis

All participants who are enrolled will be included in the analysis with the exception of participants who were enrolled in error (i.e. were ineligible).

### 10.6 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.

# 11 DATA MANAGEMENT

### 11.1 Source Data

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

### 11.2 Access to Data

Only authorised study staff will be permitted access to the password protected REDCap database where study specific data will be stored. Paper documents will be stored in a locked site with restricted access at the local site facility. On all trial-specific documents, other than the signed consent form and the letter to the GP, the participant will be referred to by the unique participant code, not by name. Access will be granted to authorised representatives of the Sponsor and the regulatory authorities to permit trial-related monitoring, audits and reports.

### 11.3 Data Recording and Record Keeping

Study Data will be entered into eCRFs within a REDCaP based system. 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.

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

Source documents will be stored at the local site or offsite under the site's control for 15 years after the completion of the trial to comply with GCP standards. eCRF data will be stored at MRINZ or offsite under MRINZ's control for 15 years after the completion of the trial to comply with GCP standards.

# 12 QUALITY ASSURANCE PROCEDURES

## 12.1 TRAINING OF STUDY SITE PERSONNEL

The Principal Investigator will ensure that appropriate training relevant to the study is given to all staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all individuals involved in the study.

## 12.2 MONITORING

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. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, 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.

# 13 SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the Investigator the serious breach will be reviewed by the Sponsor and, if appropriate, report it to the responsible ethics committee, regulatory authority, and local governance body (as applicable) within seven calendar days.

# 14 ETHICAL AND REGULATORY CONSIDERATIONS

## 14.1 DECLARATION OF HELSINKI

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

## 14.2 GUIDELINES FOR GOOD CLINICAL PRACTICE

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

## 14.3 APPROVALS

The study does not require submission to the regulatory authorities as all medications used in the study have marketing approval and are being used for the indication for which they have approval.

Ethical Submission will be made to the appropriate ethics committee / institutional review board for each study site. Approval must be granted at each site before any participants are recruited, as per local ethics committee guidelines. The ethics committee should approve all advertising used to recruit patients for the study.

The Sponsor should approve any modifications to the Participant Information Sheet and Consent Form/s that are needed, including submission to the Ethics Committee as necessary.

The co-ordinating investigator will submit all substantial amendments to the original approved documents to the ethics committee.

## 14.4 PARTICIPANT CONFIDENTIALITY

The study staff will ensure that the participant's anonymity is maintained. It is the intention of the study site to capture some participant-related information directly into an eCRF (electronic case report form) on REDCap, and to use this eCRF as source documentation. The eCRF is an encrypted secure system that is protected by unique username and password requirements for log-in, which are only provided to trained study staff.

Any personal data recorded will be regarded as confidential, and any information that would allow individual participants to be identified will not be released into the public domain. Published results will not contain any personal data that could allow identification of individual patients.

## 14.5 EXPENSES AND BENEFITS

Participants will be given reasonable reimbursement for travel costs, according to local practice and in accordance with ethical approval.

## 14.6 ETHICS AND REGULATORY REPORTING

The Principal Investigator shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the responsible Ethics Committee. In addition, an End of Trial Notification and Final Report will be submitted to the responsible Ethics Committee.

## 14.7 CHANGES TO THE PROTOCOL AND INFORMED CONSENT FORM

Study procedures will not be changed without the agreement of the Sponsor.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the responsible Ethics Committee. If a protocol amendment requires a change to the Informed Consent Form, Sponsor and the responsible Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

# 15 FINANCE AND INSURANCE

## 15.1 FUNDING

The trial will be funded by Health Research Council of New Zealand grant number 19/609. Additional funding for the Newcastle, Australia, site has been granted by the John Hunter Hospital Charitable Trust Grant Scheme.

## 15.2 INSURANCE

Participants in New Zealand may claim under the Accident Compensation Act 2001 for injury sustained during the study, if appropriate.

Insurance for Australian participants will be the standard employment indemnities provided by the University of Newcastle and Hunter New England Health.

# 16 PUBLICATION POLICY

The study findings will be published by MRINZ, in a scientific peer reviewed journal, according to the International Committee of Medical Journal Editors recommendations. The Investigators listed on page 1 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.

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# 18 APPENDICES

Appendix 1: Amendment History

Appendix 2: End of study questionnaire

## 18.1 Appendix 1: Amendment History

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made |
|---|---|---|---|---|
| 1 | 1.1 | 7th July 2020 | James Fingleton | • All references to electronic monitoring removed as electronic monitors are not going to be used for this feasibility study as they are not required to address the aims of the study.<br>• Schedule of study procedures updated to ensure all procedures in the text are represented in the table.<br>• Corrected typo on stated Tiotropium Respimat dose to match licensed dose (2.5mcg two inhalations once daily)<br>• Expanded informed consent and cultural safety sections, no change to study procedures but more accurate description<br>• Updated laboratory testing section to reflect that CRP is performed in addition to full blood count.<br>• Added repeatability information for FeNO measurement.<br>• Added explicit definition of smoking status categories.<br>• Added explicit reference to issuing of asthma management plan.<br>• Definition of exacerbation and severe exacerbation added to definitions section under safety reporting. |

## 18.2 APPENDIX 2: END OF STUDY QUESTIONNAIRE

This study has been using people's test results to guide changes to their asthma treatment. The approach is called 'treatable traits based asthma management' and also includes treating other problems that can affect asthma. If we ran a large trial testing this approach we would also treat any other problems that were found using the questionnaires you filled in today. For example, if the questionnaire suggested problems with someone's breathing pattern we would arrange for them to see a physiotherapist for advice on breathing techniques as well as continuing their inhalers.

Below are two questions about the study you have just done and a possible future study. Please put a tick in the box which is closest to how you feel.

| | Strongly Disagree | Disagree | Uncertain | Agree | Strongly Agree |
|---|---|---|---|---|---|
| I found having my medication adjusted according to my test results acceptable. | | | | | |
| I would be willing to take part in a study comparing usual care from my GP to 'treatable trait based asthma management'. | | | | | |