Protocol

RCT of an ICS/LABA reliever therapy regimen in asthma

Short title: PRACTICAL: PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist

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Synopsis

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Study design

The PRACTICAL (PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long acting beta agonist) study is a 52-week, open label, parallel group, multicentre, phase III, randomised controlled trial to compare the efficacy and safety of two asthma treatment regimens:

(i) Budesonide/formoterol Turbuhaler taken as required for relief of symptoms (ICS/fast-onset LABA reliever therapy)

(ii) Budesonide Turbuhaler as maintenance and terbutaline Turbuhaler as required for relief of symptoms (ICS maintenance and SABA reliever therapy)

In a nested substudy participants will have an electronic monitor incorporated in each Turbuhaler device to record the date and time of actuations to allow a detailed assessment of patterns of use of randomised treatments.

Study sites

Participants will be recruited from sites throughout New Zealand.

Target population

890 adult patients with asthma in whom ICS maintenance and SABA reliever therapy is recommended. 110 subjects will be included in the substudy.

Study hypothesis

The use of ICS/fast-onset LABA reliever therapy regimen has greater efficacy than ICS maintenance and SABA reliever therapy.

Objectives

Primary

To compare the efficacy of the ICS/fast-onset LABA reliever therapy regimen with the ICS maintenance and SABA reliever therapy regimen in adult patients with asthma in whom the ICS maintenance and SABA reliever therapy regimen is recommended.

Secondary

1. To compare the safety of the ICS/fast-onset LABA reliever therapy regimen with the ICS maintenance and SABA reliever therapy regimen.
2. To determine whether baseline clinical and socioeconomic characteristics such as reported beta agonist use, Th2 profile, smoking status, history of severe exacerbations or housing status predict preferential response to randomised treatments.
3. To examine patterns of inhaler use with the randomised treatments.
4. To examine the cost effectiveness of the randomised treatments.
5. To examine patient attitudes to the treatment regimens.

Study duration

Participants will be seen for the initial visit (week 0) and at weeks 4, 16, 28, 40 and 52.

Interventions

Participants will be randomised in equal proportions to one of two treatments:

(i) Budesonide/formoterol Turbuhaler 200/6µg, one actuation as required for relief of symptoms.

(ii) Budesonide Turbuhaler 200µg, one actuation twice daily and terbutaline Turbuhaler 250µg, two actuations as required for relief of symptoms

Primary outcome variable

The primary outcome variable is the rate of severe exacerbations per patient per year.

Electronic monitoring sub-study primary outcome variable

The sub-study primary outcome variable is mean daily ICS use.

Statistical methods

This will be an 'intention to treat' superiority analysis. Analysis of the primary outcome variable will be by Poisson regression with an offset for the time of observation. Over-dispersion will be evaluated prior to analysis and a corrected analysis applied if necessary.

1. Abbreviations and Definitions

ACQ	Asthma Control Questionnaire
AE	Adverse Event
ATS	American Thoracic Society
eCRF	Electronic case report form
DSMC	Data Safety Monitoring Committee
ED	Emergency Department
ERS	European Respiratory Society
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume over 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GP	General Practitioner
HDEC	Health and Disability Ethics Committee
ICS	Inhaled Corticosteroid
ICH	International Conference of Harmonisation
LABA	Long Acting Beta Agonist
NZ	New Zealand
PIS-CF	Participant Information Sheet-Consent Form
REDCAP	Research Electronic Data Capture
RCR	Roche Clinical Repository
RCT	Randomised Controlled Trial
SABA	Short Acting Beta Agonist
SAE	Serious Adverse Event
SMART	Single combination ICS/LABA inhaler for Maintenance And Reliever Therapy regimen
WPAI: Asthma	Work Productivity and Activity Impairment Questionnaire: Asthma

Exacerbation of Asthma:

An asthma exacerbation is defined by any of the following criteria:

a. Worsening asthma resulting in unplanned medical review (primary care visit, ED visit or hospital admission) and/or
b. Worsening asthma resulting in the use of systemic corticosteroids, such as a course of oral prednisone for any duration

Severe exacerbation of Asthma:

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

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

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

The ATS/ERS guidelines recommend that when severe exacerbations are an outcome variable in randomised controlled trials of medication regimens in asthma, they should be identified by the above criteria.[1]

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

High beta agonist use episode: >16 actuations of terbutaline in a 24 hour period or >8 actuations of budesonide/formoterol in a 24 hour period.[2]

These thresholds are based on the limits of beta agonist use requiring medical review defined by action plans[3,4] and supported by the short term bronchodilator equivalence of 6µg formoterol to 500µg terbutaline with repeat dosing in acute asthma.[5-7] A high beta agonist use episode is a validated measure of poor asthma control and risk of future severe exacerbations.[8]

Marked beta agonist use episode: >24 actuations of terbutaline in a 24 hour period or >12 actuations of budesonide/formoterol in a 24 hour period.

24 hour period: From midnight to midnight.

Scheduled Study Visit: This refers to any of the 6 pre-defined study visits as outlined in Section 7.

Unscheduled Study Visit: This refers to any visit arranged in addition to the scheduled visits and takes place outside of scheduled visit windows. An unscheduled visit may be arranged for one of two purposes: for dispensing of additional study medication or for consideration of withdrawal of the participant from the study (see Section 8).

2. Rationale

Asthma is a major public health problem in New Zealand (NZ)[1] with between 15% to 20% of children and adults having asthma.[9-11] The prevalence rates are among the highest in the world,[9-12] particularly in Māori and Pacific adults.[13] There are over 6,000 hospital admissions due to asthma in NZ annually.[14] Asthma is the most important cause of years lost to disability in NZ for males, and the third highest ranking cause for females.[15] The economic costs of asthma were estimated to be around NZ$825 million per year in the late 1990s. This comprises about NZ$125 million in direct costs and about NZ$700 million in indirect non-medical costs.[9]

Clinical research, health resources, and management initiatives mainly focus on severe asthma. However most adults with asthma have mild disease and there is a poorly recognised and substantial burden of disease in this group.[16-20] Globally little attention has focused on this 'silent majority' with intermittent and mild persistent asthma, yet studies of these populations show there is substantial morbidity. For example, in the OPTIMA study, 33% of asthmatic patients with mild intermittent or persistent asthma who were inhaled corticosteroid (ICS) free at baseline and throughout the study (Group A), and who had infrequent use of short acting beta-agonist (SABA), experienced a severe asthma exacerbation during the year of the study.[21] Similarly, in OPTIMA, 34% of the ICS-treated group at baseline and throughout the study (Group B) who also had infrequent use of SABA, experienced a severe exacerbation during the year of the study.[21] In two other large randomised controlled trials (RCTs) of ICS-treated patients, who did not overuse their SABA or have a severe exacerbation during the run-in period, the annual rate of severe exacerbations requiring medical intervention (hospitalisation, ED attendance or oral steroids) was 35%.[22,23]

The Global Initiative for Asthma (GINA) has established internationally accepted diagnostic and management strategies which aim to achieve optimum asthma control for individual patients.[24] However, numerous surveys in NZ and internationally show low adherence to guidelines, suboptimal management, and preventable morbidity.[16-20]

A number of factors contribute to this largely preventable morbidity in intermittent and mild persistent asthma. The most important are failure to prescribe ICS and poor adherence with ICS.[16,25-28] Since 2014, the GINA guidelines have recommended that most patients with asthma should be prescribed ICS as first line regular maintenance therapy.[24] This recommendation is based on the evidence that the regular use of ICS reduces symptoms, improves lung function, reduces severe exacerbations, prevents hospital admissions, and reduces the risk of mortality.[26,29-32]

The benefits of ICS in clinical practice are limited by poor adherence.[25-28] Poor adherence is not surprising as patients are required to take twice daily treatment regardless of whether they have symptoms. Many patients are reluctant to take ICS every day in this way.[33] Studies based on prescription refill rates show that most patients take ICS therapy infrequently, on average two to four canisters per year.[34,35] In patients admitted to hospital with severe exacerbations of asthma, ICS adherence may drop to around 50% within one week of discharge.[36] This is an important issue as poor ICS adherence contributes to asthma treatment failure, resulting in increased morbidity, risk of mortality, and consumption of healthcare resources.[25-28,31] Although adherence to ICS is higher in situations of controlled clinical trials, rates in this situation are still low. Using electronic monitoring we showed that only 39% of adult asthmatics took at least 80% of their prescribed ICS dose.[37]

The other limitation of ICS in clinical practice is reluctance of doctors to prescribe regular ICS therapy in patients who take intermittent SABA alone for symptom relief. Currently guidelines recommend the regular use of ICS in patients with symptoms on two occasions or more a month (i.e. 'Step 2' therapy).[24] Surveys show that both doctors and patients consider that this does not represent inadequately controlled asthma, or recognise the need for preventive therapy with ICS at this stage.[16-20] Recognition by primary care

practitioners that such patients are unlikely to be adherent with regular ICS treatment is likely to contribute to their reluctance to prescribe ICS.

In patients who are not adequately controlled with ICS, the addition of a long-acting beta agonist (LABA) improves clinical outcomes, including a reduction in severe exacerbations and an improvement in lung function and symptom control.[38] The addition of a LABA to ICS therapy is more effective than increasing the dose of ICS.[39] The preferred method of using a LABA with ICS therapy is through a single combination ICS/LABA inhaler.[40] This approach has the advantage of improving adherence with ICS therapy,[34,35] and avoids LABA monotherapy which may occur when ICS and LABA treatments are prescribed as separate inhalers. This is especially the case if patients use the LABA inhaler for symptom relief during periods of ICS non-adherence.[41] There is also a scientific rationale for giving an ICS and LABA together, as they have complementary actions on the complex pathophysiology of asthma and may act synergistically at a molecular level.[42]

Although regular maintenance use of a combination ICS/LABA inhaler leads to reduced symptoms and improved lung function in patients not previously treated with ICS,[38] it does not reduce severe exacerbation rates compared with maintenance ICS therapy.[43] As a result, use of both LABA and ICS as either separate inhalers or combination inhaler therapy is not recommended as first line treatment in adults with asthma without a prior trial of regular ICS with SABA reliever therapy.[24]

Over the last decade a number of strategies have been investigated to improve outcomes in mild asthma. The evidence from this research suggests a combination ICS/fast onset LABA inhaler, used solely as reliever therapy (and not for regular maintenance therapy) may represent an alternative to regular ICS with SABA reliever therapy in patients with mild asthma.[42,44,45]

These include the IMPACT trial which evaluated an intermittent ICS or oral steroid regimen guided by a symptom-based plan either alone, or in addition to, daily treatment with low dose ICS or an oral leukotriene receptor antagonist.[46] The main outcome variables were morning peak flow and severe exacerbations requiring a course of prednisone. The intermittent regimen (a 10 day course of 800µg budesonide twice daily and/or prednisone for five days for worsening asthma), had the same efficacy as regular treatment for these outcomes. However, regular ICS led to greater improvements in forced expiratory volume over 1 second (FEV_1), bronchial hyperresponsiveness, sputum eosinophil counts, exhaled nitric oxide (FeNO) and asthma control scores. The generalisability of the findings are limited by treatment of all patients with 10-14 days of high dose oral prednisone, 800µg budesonide twice daily, and 20mg zafirlukast, plus 'as needed' salbutamol reliever therapy on study entry and completion. Also, the intermittent therapy group took ICS for only a mean of 4 days in this 12 month study.

The BEST study investigated the efficacy of a symptom-driven regimen of a combination of ICS and a SABA in a single inhaler.[47] The rationale was that combination ICS/SABA therapy may result in enhanced ICS compliance in otherwise poorly ICS compliant patients who relied on SABA use, in that they would receive an ICS dose whenever they took their SABA, and the ICS dose would be self-titrated to need in worsening asthma. This study reported that in patients with mild asthma at baseline, the symptom-driven as required use of combination ICS/SABA in a single inhaler achieved equivalent efficacy to regular ICS. This suggested that mild persistent asthma may not require regular ICS, and that ICS can be taken on an intermittent basis if use is driven by the SABA within the same inhaler. This particular combined inhaler medication is not available in NZ or in other countries such as the US.

The BASALT study used a similar model of patients adjusting ICS use according to their requirement for SABA, but with separate inhalers.[48] In highly adherent patients with well or partly controlled asthma on ICS therapy, this regimen was associated with a statistically non-significant 38% reduction in risk of the primary outcome variable of time to treatment failure, compared with a 'gold standard' physician-based strategy of six-weekly adjustment of maintenance ICS dose. The symptom-driven approach of instructing patients to take two actuations of their low dose beclomethasone (ICS) inhaler every time they took a SABA resulted in a similar rate of exacerbations to a novel biomarker ICS-adjusted group, the third treatment arm. As the authors noted, symptom-based adjustment strategies are appealing because they

are simple to use, empower patients, and likely result in a lower systemic steroid burden. The use of separate ICS and SABA inhalers may have underestimated the benefits of the reliever therapy approach, as it may have missed the major potential benefit of a single combination inhaler improving adherence.

Another variation is the SMART regimen in which patients take the same combination ICS/fast onset LABA inhaler as both maintenance and reliever therapy. This is possible if the LABA has a fast onset of action similar to salbutamol. In patients with moderate to severe asthma this regimen has greater efficacy than either a SABA or LABA as reliever therapy, when taken with the same dose of ICS/LABA maintenance therapy.[2,23,49] This research provides evidence of the efficacy of ICS/fast onset LABA reliever therapy, with both the ICS and LABA components contributing to the clinical benefit, albeit in patients taking maintenance ICS/LABA therapy. Utilising electronic monitors to assess actual medication use, we have provided evidence that the reduction in severe exacerbations with the SMART regimen may be due to both the self-titrated escalation of ICS/LABA use early in the time course of an exacerbation, and greater ICS adherence.[2] There is one trial of SMART in mild to moderate asthma which showed improved asthma control compared to a higher dose of maintenance ICS plus SABA[22] confirming the efficacy of SMART therapy across a range of asthma severity.

Increasing the frequency and dose of ICS during exacerbations improves clinical outcomes. Quadrupling the ICS dose has a beneficial effect in the treatment of exacerbations of asthma.[50] In unstable asthma, increasing the dose frequency from two to four times daily, while maintaining the same total daily ICS dose provides greater efficacy.[51] By comparison, increasing the dose of ICS two-fold without increasing the frequency of dosing during exacerbations, (and with the increase occurring on average 4-5 days after asthma symptoms started to worsen), has no demonstrable clinical effect.[52,53] A systematic review of 17 studies shows that multiple doses of ICS administered at time intervals ≤30 min over 210 minutes results in faster clinical improvement than systemic steroids, increasing the probability of early ED discharge.[54] These findings apply to inhalation of budesonide 400µg every 30 min, similar to the doses taken with budesonide/formoterol metered dose inhaler in the setting of severe exacerbations in the community.[2]

This strategy is the subject of this application. It has only been explored in the SOMA trial.[55] This small study compared reliever use of a fast onset LABA (formoterol) with a fast onset ICS/LABA combination (budesonide/formoterol) as the only medications in patients with mild asthma and elevated FeNO. The primary outcome, FeNO, was lower, indicating better control of airway inflammation in the group receiving ICS/LABA reliever therapy. A limitation of the SOMA trial was that there was no regular ICS treatment comparator group.

This symptom-based ICS/LABA combination inhaler regimen is appealing because it couples ICS and LABA use to automatically ensure adherence to ICS. This has the potential to improve the frequency of daily ICS use in patients with symptomatic asthma, and to lead to a rapid increase in use during worsening asthma. Patients recognise and respond to the early signs of worsening asthma by increasing SABA use at the expense of ICS treatment.[56] The FACET study showed that there was a five to seven day period before a severe exacerbation was recognised and treated with oral steroids, during which time patients experienced deteriorating symptoms and increased their bronchodilator use, representing an opportunity to intervene.[57] In addition the rapid-onset LABA formoterol, as reliever therapy, is more efficacious than a SABA such as terbutaline,[58] or salbutamol.[59]

3. Design and objectives

3.1 Design

The PRACTICAL (PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist) study is a 52-week, open label, parallel group, phase III, multicentre RCT (see Appendix, Figure 1). The clinical trial will compare the efficacy and safety of budesonide/formoterol turbuhaler taken as required for relief of symptoms (ICS/fast-onset LABA reliever therapy) to budesonide turbuhaler for maintenance and terbutaline turbuhaler as required for relief of symptoms (ICS maintenance and SABA reliever therapy) in adult patients with asthma in whom ICS maintenance and SABA reliever therapy is recommended.

3.2 Primary objective

To compare the efficacy of the ICS/fast-onset LABA reliever therapy regimen with ICS maintenance and SABA reliever therapy regimen in adult patients with asthma in whom ICS maintenance and SABA reliever therapy is recommended.

The associated hypothesis is:

- The use of ICS/fast-onset LABA reliever therapy regimen has greater efficacy than ICS maintenance and SABA reliever therapy.

3.3 Secondary

3.3.1 To compare the safety of the ICS/fast-acting LABA reliever therapy regimen with the ICS maintenance and SABA reliever therapy regimen.

3.3.2 To determine whether baseline clinical and socioeconomic characteristics such as reported beta agonist use, Th2 profile, smoking status, history of severe exacerbations, ethnicity or housing status predict preferential response to randomised treatments.

3.3.3 To examine patterns of inhaler use with the randomised treatments.

3.3.4 To examine the cost effectiveness of the randomised treatments.

3.3.5 To examine patient attitudes to the treatment regimens.

4. Randomised treatments

4.1 Treatments

4.1.1 Participants will be randomised, stratified by site and by baseline ICS treatment with a block size of 8, 1:1 to one of two treatments:

a. Budesonide/formoterol Turbuhaler 200/6µg, one inhalation as required for relief of symptoms.

b. Budesonide Turbuhaler 200µg, one inhalation twice daily and terbutaline Turbuhaler 250µg, two inhalations as required for relief of symptoms.

4.2 Rationale

The doses of budesonide are based on its dose-response relationship in asthma,[60] and are consistent with consensus guidelines.[17] Budesonide 400µg/day achieves around 80-90% of the maximum obtainable efficacy for all major outcome measures including severe exacerbations.[60] In the initiation of ICS therapy there is no greater efficacy achieved with doses of budesonide >400µg/day.[61] For this reason consensus guidelines recommend that ICS therapy is initiated with a dose of budesonide of 400µg/day or equivalent.[24] The dose of budesonide/formoterol 200/6µg one inhalation as required for symptom relief, is one of the doses recommended in the Single combination ICS/LABA inhaler for Maintenance And Reliever Therapy (SMART) regimen. The 250µg terbutaline dose, taken 2 inhalations for relief of symptoms, represents that recommended for use in NZ.

4.3 Inhaler technique

4.3.1 At the first visit, participants will be educated on correct inhaler technique, with a demonstration and written instructions.

4.3.2 Inhaler technique will be assessed at study visits 1-5.

4.4 Asthma Action Plans

4.4.1 All participants will be given education on medication use and inhaler technique, and a written asthma action plan relating to their randomised group. Participants will be provided with modified versions of the "Symbicort SMART Asthma Action Plan" promoted by the National Asthma Council of Australia.[62] The purpose of providing these plans is to both reinforce the randomised treatment regimens and provide written instructions on what actions the participants should take in the situation of worsening asthma, in particular when to seek general practitioner (GP) review and emergency medical care.

4.4.2 Participants will not be required to measure their peak flow or to fill in a record card every day as this would prompt the participants to take their medicines regularly and promote adherence. These effects would reduce the chance of seeing a difference between regular and reliever ICS regimens which occur in "real-world" scenarios. Those subjects who already monitor their peak flows on entry to the study will be advised to continue to do so with an action plan incorporating peak flow use. For the purpose of this study, a drop in peak flow to <60% of recent best will signify a deterioration in asthma control, requiring contact with a doctor.

4.4.3 Participants will remain under the usual care of their GP for the duration of the study.

4.5 Other inhalers

4.5.1 Participants will be advised not to share their allocated inhalers

4.5.2 Participants will be advised not to use other non-study inhalers or nebulisers, unless indicated by their doctor. If they do use non-study inhalers or nebulisers they will be asked to document this.

4.5.3 At the first study visit participants will have their regular inhalers collected by investigators.

4.6 Electronic Monitoring sub-study

4.6.1 A nested sub-study will be undertaken at the Medical Research Institute of New Zealand site, where a total of 110 randomised participants will have electronic monitors incorporated in each turbuhaler device.

4.6.2 Electronic monitors will record the date and time of every actuation.

4.6.3 The participants will be told that they are using a modified inhaler that has been produced specifically for this sub-study to count the precise number and timing of doses used during the study period. This will provide a reason for the need to avoid using other inhalers. Participants will be told that the purpose of the sub-study is to compare the benefits of the two treatment regimens and to determine whether the patterns of use influence outcome.

4.6.4 For further detail on electronic monitoring see section 12.

4.6.5 Participants in the substudy will have an optional additional blood sample collected for full blood count at visit 6 (week 52). If they withdraw from the study early the additional blood sample will not be collected.

4.7 Other written information

4.7.1 Each participant will be provided with a study card indicating that they are participating in the trial. This card will include the contact details for the investigators and the date and time of the next study visit, as well as space to document any courses of systemic corticosteroids (e.g. prednisone) taken or acute medical visits (e.g. GP, ED or Afterhours Clinics).

4.7.2 Written information will be provided specific to study involvement. This will include the following instructions:

4.7.2.1 When to contact the investigators (see section 8.3.1).

4.7.2.2 How to care for the monitors (for participants allocated to receive electronic monitoring only).

4.8 Participant information on withdrawal criteria

4.8.1 Participants will be informed that they may be withdrawn from the study if the investigator is concerned about their safety.

4.8.2 Participants will not be informed of the criteria for consideration of need to withdraw.

4.8.3 Participants will be informed they can withdraw from the study at any stage. Arrangements for patient follow-up by the participant's GP will be made.

5. Participants

890 patients with asthma will be recruited into the study.

5.1 Inclusion criteria

5.1.1 Adults aged 18 to 75 years.

5.1.2 Self-report of a doctor's diagnosis of asthma.

5.1.3 a. Not used ICS in the 12 weeks prior to entry into the study and

- asthma symptoms or need for SABA ≥ two occasions in the last 4 weeks, or
- waking due to asthma ≥ once in the last 4 weeks, or
- exacerbation requiring oral corticosteroids in the last 52 weeks

or

b. Used ICS in the 12 weeks prior to entry in the study, and prescribed ICS at low or moderate doses (≤500µg/day fluticasone propionate or small particle formulation beclomethasone diproprionate (QVAR); ≤800 µg/day budesonide; ≤1,000 µg/day beclomethasone diproprionate (Beclazone)), and:

i. has partly or well controlled asthma as defined by GINA guidelines (see Table 1),

OR

ii. has uncontrolled asthma as defined by GINA guidelines (see Table 1) and either poor adherence to ICS and/ or unsatisfactory inhaler technique (see Table 2 and 3).

The GINA guidelines recommend that both patient treatment groups (a and b) should receive ICS maintenance and SABA reliever therapy.

5.1.4 Willing and able to give informed consent for participation in the trial.

5.1.5 In the investigator's opinion, able and willing to comply with all trial requirements.

5.1.6 Willing to allow their GP (and specialist if appropriate) to be notified of participation in the trial.

Table 1: GINA level of asthma symptom control[24]

In the past 4 weeks, has the patient had:	Well controlled	Partly controlled	Uncontrolled
Daytime symptoms more than twice/week (yes or no)	None of these	1-2 of these	3-4 of these
Any night waking due to asthma (yes or no)			
Reliever needed* more than twice/week (yes or no)			
Any activity limitation due to asthma (yes or no)			

* Excludes reliever taken before exercise.

Table 2: Assessment of adherence

Assessment	Calculation	Criteria for Inclusion
Many people don't take their medication as prescribed. In the last four weeks: Q. How many days a week would you have taken your preventer medication? [Ow] A. None at all? One day a week? Two days a week? (etc). Q. How many times a day would you take it? [O_D] A. Morning only? Evening only? Morning and evening? (or other) Q. Each time, how many puffs would you take? [A_T] A. One? Two? (etc, depending on the prescribed dose). Q. How many times a day should you take it, according to your prescription? [ODP] A. Morning only? Evening only? Morning and evening? (or other) Q. Each time, how many puffs should you take, according to your prescription? [A_{TP}]	$((Ow/7)*(O_D/O_{DP})*(A_T/A_{TP}))*100=$ % adherence Where: Ow= days taken per week O_D= occasions taken per day O_{DP}= occasions prescribed per day A_T= actuations taken per occasion A_{TP}= actuations prescribed per occasion	≤80% adherence results in inclusion criterion 5.1.3 b ii being fulfilled.

Table 3: Assessment of inhaler technique

Assessment	Criteria for Inclusion
The patient may be deemed to have unsatisfactory inhaler* technique if: 1. Their overall ICS inhaler technique is judged to be unsatisfactory (at the discretion of the investigator) OR 2. They do not complete all essential criteria, as per the modified National Asthma Council Australia checklist in the Appendix (Figure 6) * Note inhaler technique at Visit 1 is assessed only on the participant's ICS inhaler.	Unsatisfactory technique results in inclusion criterion 5.1.3 b ii being fulfilled.

5.2 Exclusion criteria

5.2.1 Self-reported use of LABA, leukotriene receptor antagonist, theophylline, anticholinergic agent or cromone as maintenance therapy in the 12 weeks before potential study entry. Nasal corticosteroid therapy is permitted.

5.2.2 Self-reported past admission to the Intensive Care Unit (ICU) with life-threatening asthma (representing patients at highest risk of adverse asthma outcomes).

5.2.3 Self-reported treatment with oral prednisone or other systemic corticosteroids in the six weeks before potential study entry (representing recent unstable asthma).

5.2.4 A home supply of prednisone for use in worsening asthma, as part of a current asthma plan.

5.2.5 Self-reported diagnosis of COPD, bronchiectasis or interstitial lung disease.

5.2.6 Self-reported greater than 20 pack year smoking history, or onset of respiratory symptoms after the age of 40 years in current or ex-smokers with ≥10 pack year history.

5.2.7 Self-reported current pregnancy or breast feeding at the time of enrolment or planned pregnancy within the study period.

5.2.8 Unwilling or unable to switch from current asthma treatment regimen.

5.2.9 Other illness(es) likely to compromise participant safety or impact on the feasibility of results, at the discretion of the investigator (examples include unstable coronary disease and malignancy).

5.3 Participant enrolment

5.3.1 Potentially eligible participants will be allocated an enrolment number (sequential number at that site prefaced with the letter E and the designated site number). Sites will be responsible for documenting whether potentially eligible participants are excluded and why, on a screening log.

5.3.2 When a participant is randomised they will be given a randomisation number (sequential number at that site prefaced with the letter R and the designated site number).

5.3.3 Randomisation codes will be sequentially assigned as soon as participants are confirmed as eligible for randomisation.

5.3.4 Enrolment and randomisation numbers cannot be re-used.

5.4 Participant withdrawal criteria

5.4.1 Participants will be withdrawn from the study and discontinue randomised treatment if:

5.4.1.1 The participant was found to be incorrectly enrolled in the study (see Section 5).

5.4.1.2 The participant decides to discontinue (withdrawal of informed consent).

5.4.1.3 Prescribed randomised treatment is increased by the participant's GP or other healthcare provider for >14 consecutive days during the study period*

5.4.1.4 The participant becomes pregnant.

5.4.1.5 Any safety reason as judged by the investigator. After each asthma related hospital admission there will be central review as to whether it is in the patient's interests to withdraw from the study.

*Randomised treatment Modifications are defined as an increase in the participants' randomised asthma inhaler regimen and/ or the addition of medications to aid asthma control including SABA, ICS/LABA, ICS, LABA, leukotriene receptor antagonists, mast cell stabilisers, theophylline and monoclonal antibody therapy.

Note that if a modification results in a decrease in the participants' randomised asthma inhaler regimen this is not a cause for withdrawal. The change is to be documented on the eCRF. Participants who have had a reduction will be encouraged by the investigator to return to their randomised regimen.

5.5 Participant withdrawal procedure

5.5.1 Participants identified as needing withdrawal at a study visit:

5.5.1.1 The visit will be conducted as a Visit 6.

5.5.1.2 An exception to this is if the participant declines consent to continue the study visit.

5.5.1.3 In addition to Visit 6 procedures, reason for withdrawal must be documented. If possible, participants who decide to withdraw will be asked why.

5.5.2 Participants identified as needing to be withdrawn between study visits:

5.5.2.1 An unscheduled study visit should be booked as soon as practically possible (see Section 8).

5.5.2.2 If, at this visit the participant is identified as needing to be withdrawn, the visit will be conducted as a Visit 6.

5.5.2.3 In addition to Visit 6 procedures, reason for withdrawal must be documented. If possible, participants who decide to withdraw will be asked why.

5.5.2.4 At withdrawal from the study participants will be treated according to local medical practice.

6. Randomisation and blinding

6.1 Randomisation

6.1.1 Participants will be block randomised, block size eight per site.

6.1.2 Randomisation will be stratified according to site and whether participants used ICS therapy prior to enrolment or not.

6.1.3 A computer-generated randomisation number sequence will be created by the study statistician, independent of the investigators undertaking recruitment and subsequent visits.

6.1.4 The electronic case report form (eCRF) system will conceal the allocations and will release a participant's randomisation outcome at the time of randomisation. The randomisation schedule will be accessed only by the study statistician and the eCRF provider; study staff will not have access to the randomisation schedule.

6.1.5 Detailed instructions regarding use of the eCRF system will be provided in a manual.

6.2 Blinding

6.2.1 A participant's treatment allocation will only be revealed to the researchers when that participant is randomised via the eCRF.

6.2.2 There is no blinding to allocated intervention in this study. Study investigators, study staff and participants will be aware of the treatment allocation. Blinding is not being performed, in order to maintain the potential 'real world' advantage of the ICS/LABA reliever therapy regimen, i.e. the use of a single medication and no requirement for regular inhaler use.

6.2.3 The study statistician will be blinded while performing the primary analysis of the primary outcome variable.

7. Scheduled study visits

7.1 Visit overview

Table 4: Visit overview

Visit Number	**Consent & Enrolment**	**1**	**2**	**3**	**4**	**5**	**6**	**Unscheduled visit**
Week	≦0*	0	4	16	28	40	52	As required
Day	≦0*	0	28	112	196	280	364	As required
Visit Window (Days)	n/a	n/a	±5	±5	±5	±5	±5	n/a
Pre dispensing monitor check^		X	X	X	X	X	X	
Written informed consent	X							
Optional Future Unspecified Research Written Informed consent+	X							
Inclusion/Exclusion criteria check	X	X*						
ACQ-5		X	X	X	X	X	X	
Beliefs about Medicines Questionnaire		X					X	
WPAI: Asthma Questionnaire		X		X			X	
Housing Status Questions		X						
VOLP Questionnaire							X	
AQLQ(S) Questionnaire							X	
EQ-5D-5L Questionnaire							X	
Participant attitudes, preferences and reliever use questionnaire and discrete choice experiment***							X	
Medical history & demographics		X						
Weight and height		X						
FeNO#		X		X			X	
Spirometry		X		X			X	
Blood test for periostin+		X						
Blood test for full blood count		X					X^	
Blood test for other biomarkers+		X£						
Randomisation		X						
Study ICS inhaler technique assessment			X	X	X	X	X	
Participant education & issuing of study inhalers		X	X	X	X	X		
Issue written asthma action plan and other written information		X						
Inform GP of study enrolment		X						
Review: - Exacerbations - AEs - SAEs** - Medication changes - Issues with equipment use^			X	X	X	X	X	X
Returned electronic monitors:^			X	X	X	X	X	X

- Check for damage - Upload from monitor via USB cable								
If participant is to be withdrawn, documentation of cause and notification to GP and Sponsor			X	X	X	X	X	X
Inform GP and Sponsor of study completion							X	

*Performed if consent and enrolment done on a different day to Visit 1. ^Participants allocated to electronic monitoring only. #Performed prior to spirometry. n/a: not applicable. +Participants subgroup recruited at MRINZ only. £In participants who consent to the optional future unspecified research only. ** Investigator to inform Sponsor within 24 hours of becoming aware of an SAE (for further detail see Section 13). ***to be completed by a subgroup of participants at selected sites, subsequent to HDEC approval.

7.2 Written informed consent

7.2.1 Is to take place according to ICH GCP guidelines, prior to any study specific procedures.

7.3 Inclusion/exclusion criteria check

7.3.1 Please see Section 5 for criteria.

7.4 ACQ-5[63]

7.4.1 Will be administered prior to history taking or spirometry.

7.4.2 The questionnaires will be in 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.

7.5 Beliefs about Medicines Questionnaire[32]

7.5.1 The questionnaire will be in 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.

7.6 Work Productivity and Activity Impairment Questionnaire: Asthma

7.6.1 The questionnaire will be in 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.

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

7.7.1 The questionnaire will be in 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.

7.8 Valuation of Lost Productivity Questionnaire (VOLP)

7.8.1 The questionnaire will be in paper format and self-administered. Where this is not possible the investigator may read and/or record answers for the participant, however it must be documented that this took place.

7.9 EQ-5D-5L Work Productivity and Activity Impairment Questionnaire: Asthma

7.9.1 The questionnaire will be in 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.

7.10 Housing Status Questions

7.10.1 The investigator will administer the housing status questions at Visit 1 (see Appendix, Figure 8 for more detail). The questions will be in paper format, with the investigator asking each individual question and providing the answer categories that are available to the participant. The investigator will record the answers given by the participant.

7.11 Participant attitudes, preferences, and reliever use questionnaire and discrete choice experiment (DCE)

7.11.1 The questionnaire is optional and will be provided only to those participants completing the study after the questionnaire has been approved by HDEC. The questionnaire will be conducted at selected study sites, based on a feasibility assessment by the Sponsor.

7.11.2 The questionnaire items will be developed from review of the literature and investigator group consensus. The questionnaire will be piloted in a sample of participants who have completed the PRACTICAL study.

7.11.3 The questions will be administered through a programme written in REDCap (Research Electronic Data Capture) and administered at Visit 6. The participant will be provided with a sheet explaining key terms. The participant should read and fill in the questionnaire 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. If the participant is unable to complete the questionnaire during V6 they may complete the questionnaire via online survey at a later date.

7.11.4 The DCE is optional and will be provided only to those participants completing the study after the DCE has been approved by HDEC. The DCE will be conducted at selected study sites, based on a feasibility assessment by the Sponsor.

7.11.5 Further details on DCE methodology and statistical analysis are provided in a separate document, however a description of the discrete choice methodology we will use is explained at https://www.1000minds.com/conjoint-analysis/pairwise-comparisons-method. Attributes and levels for the DCE will be selected from inherent properties of the treatment regimen or trial outcome measures with reference to the literature. The DCE will be piloted in a sample of participants who have completed the PRACTICAL study.

7.11.6 The DCE will be administered through the 1000minds online portal (1000minds Ltd, Dunedin, NZ) at Visit 6. The participant should complete the DCE 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. If the participant is unable to complete the DCE during V6 they may complete the questionnaire via online survey at a later date.

7.12 Medical history and demographics

7.12.1 Date of birth, age and sex.

7.12.2 National Health Index (NHI). The NHI number will be entered into the eCRF and used by the MRINZ to centrally validate exacerbation outcome data relating to hospital attendance and/or admission.

7.12.3 Address/ housing history:

7.12.3.1 Current full street address

7.12.3.2 Number of times the participant has moved house in the five years pre-Visit 1.

7.12.4 Smoking history:

7.12.4.1 Current, ex or never

7.12.4.2 Pack years

7.12.5 Asthma history:

7.12.5.1 Age of diagnosis

7.12.5.2 Whether the participant currently uses an asthma action plan, and whether it is with or without peak flow measurement

7.12.5.3 Whether the participant is currently prescribed ICS, which product and at what daily dose

7.12.5.4 Number of courses of systemic corticosteroids for asthma in the last year, and number of days per course

7.12.5.5 Use of systemic corticosteroids to treat other conditions in the last year and the number of days per course

7.12.5.6 Number of ED visits for asthma in the last year and for each visit whether a systemic corticosteroid was administered

7.12.5.7 Number of hospital admissions for asthma in the last year

7.12.5.8 Number of severe exacerbations (ATS/ERS criteria) for asthma in the past year

7.12.5.9 Whether the participant has ever previously been prescribed ICS inhalers, and if so when last used.

7.12.6 Other medical conditions and medications

7.12.7 Highest education level, job title and job description

7.13 Weight and height

7.13.1 Will be measured without shoes on and using site equipment.

7.14 FeNO

7.14.1 Performed as a single test as per ATS/ERS criteria[64] and manufacturer instructions prior to any spirometry. NIOX Vero FeNO devices will be used at each study site.

7.15 Spirometry

7.15.1 FEV_1 and forced vital capacity (FVC) will be performed according to ATS/ERS criteria[65] using a hand-held spirometer. For further detail see the study manual.

7.15.2 Study participants will not be required to with-hold from using their inhalers prior to the study appointments and spirometry testing.

7.15.3 Reversibility testing is not required at any visit.

7.16 Blood test for full blood count and periostin

7.16.1 Full blood count sample at Visit 1 (week 0).

7.16.2 Optional full blood count sample at Visit 6 (week 52) for participants in the electronic monitoring sub-study only.

7.16.3 Periostin samples will be taken at visit 1 (week 0). Periostin samples will be taken in a subgroup of participants recruited from the MRINZ only.

7.16.4 Please see study manual for processing instructions.

7.17 Optional blood test for future unspecified research

7.17.1 An optional blood test for future unspecified research will be taken at Visit 1 (week 0). This is to collect samples to investigate the utility of novel serum biomarkers. One additional blood sample of up to 10ml (resulting in 2 serum aliquots of up to 3ml each) will be taken from a subgroup of participants recruited at the Medical Research Institute of New Zealand and who consent to this portion of the study only. The sample will be taken at the same time as the main study blood tests, therefore the participant will not have to undergo a separate blood test procedure.

7.17.2 There will be a separate PIS-CF for this subgroup which will contain information to describe to the participant the objectives, methods, and potential hazards of provision of samples for future unspecified research and the provision samples. Participants will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason. A separate, specific signature will be required to document a participant's agreement to provide optional specimens. Participants who decline to participate will not provide a separate signature. Participants may still take part in the main PRACTICAL study, without having to consent to the optional future unspecified research sample. This consent will be administered in accordance with NZ HDEC and Ministry of Health guidelines.

7.17.3 For sampling procedures, handling (including sample withdrawal), storage conditions and shipment instructions, please see the laboratory manual. A separately developed statistical analysis plan will contain further information on the future unspecified research aims and analysis.

7.18 Randomisation

7.18.1 For details on randomisation please see Section 6.

7.18.2 The eCRF system will allocate a unique randomisation number to each participant. Investigators will allocate study medication to each participant based on their randomisation outcome. The Investigator will record the randomisation number on each dispensed inhaler.

7.18.3 If a participant withdraws from the study their randomisation number cannot be re-used.

7.18.4 If a participant is randomised and subsequently found not to meet the inclusion criteria or found to fulfil an exclusion criterion (Sections 5.1 and 5.2), or is allocated incorrect study medication, contact needs to be made with the sponsor as soon as practical.

7.19 Study turbuhaler technique assessment

7.19.1 At Visit 1, study Turbuhaler technique will be assessed according to the checklist in the Appendix (Figure 7), after education has been provided on the use of the study inhalers, to check that the participant has the correct technique.

7.19.2 At Visits 2-6 study Turbuhaler technique will be assessed according to the checklist in the Appendix (Figure 7), prior to participant education.

7.20 Participant education, action plans and medication dispensing

7.20.1 Visit 1 only:

7.20.1.1 Participants will be given a written action plan:

7.20.1.1.1 Specific to their regimen (see Section 4)

7.20.1.1.2 If participants use a peak flow meter and are able to provide the investigator with their usual best peak flow value, this will be documented and incorporated into their action plan, such that a drop in peak flow to <60% of recent best will signify a deterioration in asthma control requiring contact with a doctor.

7.20.1.1.3 Participants will be neither encouraged nor discouraged from using their reliever inhaler before exercise to prevent exercise induced asthma.

7.20.1.2 Prevention of other inhaled medication use:

7.20.1.2.1 Participants will be asked to stop using their current inhalers following visit 1 and to store them somewhere securely at home, dispose of them, or hand them to the investigator

7.20.1.2.2 Participants will be advised not to use other non-study inhalers or nebulisers, unless indicated by their doctor. If they do use non-study inhalers or nebulisers they will be asked to document the date, time and dose.

7.20.1.2.3 Participants will be advised not to share their study allocated inhalers.

7.20.1.3 Participants will be informed:

7.20.1.3.1 Participants will be informed that if there is any concern about their safety during the study the investigator may withdraw them.

7.20.1.4 Participants allocated to receive study monitors will be informed:

7.20.1.4.1 Monitors can record if they have been removed/tampered with.

7.20.1.4.2 Monitors are not to be removed, tampered with or gotten wet.

7.20.1.4.3 That they are using a modified inhaler that has been produced specifically for this sub-study to count the precise number and timing of doses used during the study period. This will provide a reason for the need to avoid using other inhalers. Participants will be told that the purpose of the sub-study is to compare the benefits of the two treatment regimens and to determine whether the patterns of use influence outcome.

7.20.2 Visits 1-5:

7.20.2.1 Inhaler technique:

7.20.2.1.1 Satisfactory inhaler technique will be taught based on written information sheets.

7.20.2.2 Participants will be reminded:

7.20.2.2.1 The instructions of the asthma 'action' plan.

7.20.2.2.2 They are to take all dispensed inhalers (including used or empty inhalers) to their next study visit.

7.20.2.3 Participants allocated to electronic monitoring will be reminded:

7.20.2.3.1 Monitors can record if they have been removed/tampered with.

7.20.2.3.2 Monitors are not to be removed, tampered with or gotten wet.

Note that data uploaded from the monitors is **not** to be discussed with the participant or used to guide discussion around compliance with the asthma 'action' plan.

7.20.2.4 Participants will be advised to contact the investigator if:

7.20.2.4.1 Their GP or usual healthcare provider makes any changes to their randomised treatment.

7.20.2.4.2 They are concerned they will run out of inhaler medications prior to the next study visit.

7.20.2.4.3 They are concerned the allocated monitors or inhalers are not operating correctly (participants allocated to electronic monitoring only).

7.20.2.4.4 They wish to withdraw from the study.

7.20.2.4.5 They become pregnant (female participants only).

7.20.2.5 Medication dispensing

7.20.2.5.1 Participants will be issued with 0 to 5 new turbuhalers at each visit (depending on the randomised treatment, time to the next visit and turbuhaler use during the previous treatment period). For more detail see the study manual.

7.21 Dispense monitors with pre-dispensing monitor check, for participants allocated to electronic monitoring only

7.21.1 Visit 1: Monitors must be tested after randomisation and prior to dispensing

7.21.2 Visit 2-5: Monitors must be tested by the investigator on day of visit

7.21.3 Please see Section 12 for further detail.

7.22 Review

7.22.1 For AEs and SAEs, with associated documentation (AE/SAE reporting as required, see Section 13).

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

Any medical review (GP/ED/hospitalisation)

Any systemic corticosteroids such as oral prednisone taken

Whether any other medications were used for asthma (other than those allocated as part of the randomised study regimen)

Any change in medication (update medication log)

Any concerns with equipment use (including monitors and inhalers)

7.22.3 Hospital-based medical attendances will be verified by documentation of attendance provided by the participant, their GP or by searching the hospital database. For more detail see the study manual.

7.23 Returned inhalers

7.23.1 Inhaler medication returned at the study visits will be stored as a reserve supply, until sponsor confirms it may be destroyed.

7.24 Returned inhalers with monitors, from participants allocated to electronic monitoring only

7.24.1 Perform collection check

7.24.2 Upload of data via USB cable

7.24.3 For further detail see section 12

7.25 GP communication and study completion

7.25.1 The participant's GP must be informed when the participant is enrolled into the study and after completion of the study.

7.25.2 At completion of study participants will be treated according to local medical practice.

7.26 End of study

7.26.1 The end of the study is defined as database lock, subsequent to the last visit of the last participant undergoing the study.

7.26.2 The Sponsor will stop the study prematurely if any safety concerns are apparent, either arising from this study, or if the Sponsor is informed of any safety issues arising outside of this study, including but not limited to safety concerns regarding the study medications. Sites will be informed of early termination of the study due to safety concerns, as soon as possible.

7.26.3 In the case of safety concerns arising during the study, investigators may deviate from the protocol in order to ensure the health and wellbeing of participants. The Sponsor must be informed of any cases where the protocol is not adhered to and the reasons for non-adherence, as soon as possible. Non-adherence will be reported to the appropriate ethics committees and regulatory authorities in line with local requirements.

7.27 Visit windows

7.27.1 Study visits are to be scheduled to occur within ±5 days of their due date; however if this is not possible for some reason or they have to be held early or postponed the visit window may be extended at the investigator's discretion.

7.27.2 Participants may also arrange to attend an additional unscheduled appointment at any time if their medications are running low or they are concerned about their inhaler or monitor function (Section 8).

7.27.3 If a participant fails to attend their scheduled study appointments at the study clinics they will be contacted by telephone and arrangements made to reschedule the missed appointment.

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8. Unscheduled study visits

8.1 Unscheduled visit for consideration of withdrawal

8.1.1 Should an investigator become aware that a participant wishes to withdraw or may require withdrawal from the study between study visits they will request attendance at an unscheduled visit.

8.1.2 This is to take place as soon as practically possible.

8.1.3 Unscheduled visits will not take the place of the participant's usual medical care.

8.1.4 Participants will be asked to bring all dispensed inhalers and monitors to the visit.

8.1.5 The following steps will be taken:

8.1.5.1 Review

8.1.5.1.1 For AEs and SAEs, with associated documentation (medical condition log and AE/SAE reporting as required, see Section 13)

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

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

8.1.5.2 Returned inhalers and monitors, for participants allocated to electronic monitoring only

8.1.5.2.1 Perform collection check

8.1.5.2.2 Upload of data via USB cable

8.1.5.2.3 For further detail see section 12

8.1.6 If the participant is withdrawn:

8.1.6.1 The visit will become a Visit 6 (final visit).

8.1.6.2 An exception to this is if the participant declines consent to continue the study visit.

8.1.6.3 In addition to Visit 6 procedures, reason for withdrawal must be documented. If possible, participants who decide to withdraw will be asked why.

8.1.6.4 The sponsor must be informed of the withdrawal as soon as is practical, via the eCRF system.

8.1.7 If the participant is not withdrawn

8.1.7.1 All inhalers the participant brought to the visit will be returned to them.

8.1.7.2 The participant will continue on their randomised regimen and attend their next scheduled visit.

8.2 Unscheduled visit for dispensing of trial medication or review of equipment

8.2.1 This may occur if a participant reports that:

8.2.1.1 They are concerned they will run out of inhaler medication prior to the next study visit due to loss of inhaler(s).

8.2.1.2 They are concerned they will run out of inhaler medication prior to the next study visit due to high use of study inhaler(s).

8.2.1.3 They are concerned the allocated inhalers are not operating correctly.

8.2.1.4 They are concerned the allocated monitors are not operating correctly, for participants allocated to electronic monitoring only.

8.2.2 This is to take place as soon as practically possible

8.2.3 The following steps will be taken in those who attend this visit because they are concerned they will run out of inhaler medication prior to the next study visit due to high use of study inhaler(s) (8.2.3.1):

8.2.3.1 Review

8.2.3.1.1 For AEs and SAEs, with associated documentation (medical condition log and AE/SAE reporting as required, see Section 13).

8.2.3.1.2 If participants self-report high use (>16 puffs of Terbutaline or >8 puffs of Budesonide/formoterol Turbuhaler in a 24 hour period) without medical review in the past 7 days, they will be: advised to seek medical review from their GP or usual healthcare provider, in accordance with their action plan. If it is apparent that there may be difficulty obtaining such a medical review in a timely manner, then they will be given a 5 day prescription for prednisone (in accordance with their action plan), and advised to seek further medical review if their symptoms do not improve. If the investigator considers that the participant requires urgent medical assessment and treatment, then the investigator will refer to the appropriate after hours/ ED service.

8.2.3.2 Returned inhalers and monitors, for participants allocated to electronic monitoring only

8.2.3.2.1 Perform collection check

8.2.3.2.2 Upload of data via USB cable

8.2.3.2.3 For further detail see section 12

8.3 Participant contact between visits

8.3.1 Participants are advised to contact the investigator if:

8.3.1.1 A healthcare provider makes any changes to their randomised treatment.

8.3.1.2 They are concerned they will run out of inhaler medication prior to the next study visit.

8.3.1.3 They are concerned the allocated inhalers are not operating correctly.

8.3.1.4 They are concerned the allocated monitors are not operating correctly, for participants allocated to electronic monitoring only.

8.3.1.5 They wish to withdraw from the study.

8.3.1.6 They become pregnant during the study (female participants only)

8.3.2 Investigators will contact the participant if:

8.3.2.1 The participant forgets to bring their inhalers to a visit (in which case every effort should be made to have them returned to the investigator as soon as possible, e.g. via a self-addressed courier bag).

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9. Study outcome measures

9.1 Overall study outcomes:

9.1.1 **Primary:**

Rate of severe asthma exacerbations per patient per year.

A severe exacerbation, as defined by ATS/ERS guideline,[1] is:

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

b. Hospitalisation or ED visit because of asthma, requiring systemic corticosteroids.

9.1.2 **Secondary:**

9.1.2.1 Clinical outcomes

9.1.2.1.1 Rate of asthma exacerbations per patient per year.

9.1.2.1.2 Time to first severe exacerbation of asthma.

9.1.2.1.3 Time to first exacerbation of asthma.

9.1.2.1.4 The proportion of severe exacerbations defined by each of the above criteria.

9.1.2.1.5 The proportion of participants with at least one severe exacerbation.

9.1.2.1.6 ACQ-5.[63]

9.1.2.1.7 On-treatment FEV1, i.e. without withholding of bronchodilator medication.[64]

9.1.2.1.8 On-treatment FEV_1 percentage predicted, i.e. without withholding of bronchodilator medication.[64]

9.1.2.1.9 FeNO.[65]

9.1.2.1.10 Proportion of participants withdrawn and reason.*

*Proportion of participants withdrawn due to "treatment failure" will also be presented. Treatment failure is defined as withdrawal due to 5.4.1.3 or withdrawal due to uncontrolled asthma under the randomised regimen resulting in safety concerns, as judged by the investigator (subgroup of 5.4.1.5).

9.1.2.2 Adverse events

9.1.2.2.1 Adverse events.

9.1.2.2.2 Serious adverse events.

9.1.2.3 Cost-effectiveness

9.1.2.3.1 The medical costs [the following represent current indicative figures, which will be updated to current actual figures at the time of analysis; medications (terbutaline $22/turbuhaler, budesonide $19/turbuhaler, budesonide/formoterol $60/turbuhaler), emergency medical ($86/visit) and ED visits ($339/visit), and hospital admissions (medical ward $1,194/day, high dependency unit $2,763/day, ICU $5,570/day)] and non-medical costs (days off work $167/day) will be calculated for each treatment regimen. The cost-effectiveness data collected will allow extrapolation to future pricing models with lower cost generic medications.

9.1.2.3.2 Work Productivity and Activity Impairment questionnaire: Asthma.

9.1.2.4 Patient attitudes:

9.1.2.4.1 Beliefs about Medicines Questionnaire[32]

9.1.2.4.2 Participant attitudes, preferences, and reliever use questionnaire and DCE.

9.2 Electronic monitoring sub-study outcomes

9.2.1 **Primary:**

Mean ICS dose per day (budesonide µg/day).

This outcome variable will enable any differences in mean ICS use to be determined between the two regimens, and whether any differences in efficacy between the two regimens are associated with differences in mean ICS use.

9.2.2 **Secondary:**

9.2.2.1 Proportion of participants with at least one day of no ICS use.

9.2.2.2 Number of days of no ICS use.

9.2.2.3 Number of ≥7 consecutive day periods of no ICS use

9.2.2.4 Number of ≥14 consecutive day periods of no ICS use.

9.2.2.5 Longest duration of no ICS use (days)

9.2.2.6 Corticosteroid use:

9.2.2.6.1 Total oral corticosteroid dose.

9.2.2.6.2 Number of courses of oral corticosteroid per year

9.2.2.6.3 Composite systemic corticosteroid exposure/year in which the total ICS dose/year, converted to oral prednisone-equivalent dose for systemic effects on adrenal function, is added to the oral prednisone dose per year, as previously defined (budesonide 5000µg inhaled equivalent to prednisone 10mg oral).[66] For other systemic corticosteroids, conversion to prednisone-equivalent doses will be

undertaken by reference to the British National Formulary (Appendix).

9.2.2.7 High beta agonist use, defined as >16 actuations of terbutaline or >8 actuations of budesonide/formoterol per 24 hour period.[2]

9.2.2.7.1 Proportion of participants with at least one episode of high use.

9.2.2.7.2 Number of days of high use.

9.2.2.7.3 Number of days of high use in participants with at least one day of high use.

9.2.2.7.4 Number of high beta agonist use episodes without medical review in the following 48 hour period, 7 day period and 14 day period in participants who had at least one high beta agonist use episode, as previously defined.[2]

9.2.2.7.5 Proportion of high use episodes without medical review within 48 hours, 7 days and 14 days.

9.2.2.8 Marked beta agonist overuse, defined as >24 actuations of terbutaline or >12 actuations of budesonide/formoterol per 24 hour period, as previously defined.[2]

9.2.2.8.1 Proportion of participants with at least one episode of marked overuse.

9.2.2.8.2 Number of days of marked overuse.

9.2.2.8.3 Number of days of marked use in participants with at least one day of marked overuse.

9.2.2.8.4 Number of marked beta agonist use episodes without medical review in the following 48 hour period, 7 day period and 14 day period in participants who had at least one marked beta agonist use episode.

9.2.2.8.5 Proportion of marked use episodes without medical review within 48 hours, 7 days and 14 days.

9.2.2.9 Maximum number of beta agonist actuations in a 24 hour period.

9.2.2.10 Use of study medications in the 14 days prior to severe exacerbations, as previously defined,[67] with graphical presentation of the median (interquartile range) daily medication use for the randomised groups, and the medication use for the individual participants within each randomised group.

9.2.2.11 Blood eosinophil count at visit 6, adjusted for baseline count.

10. Sample size calculation

The primary outcome variable is the rate of severe asthma exacerbations per patient per year. Assuming a drop-out rate of 10%, 890 patients will be recruited to enable a sample size of 400 completed patients in each treatment arm, resulting in 90% power, alpha 5%, to detect a 38% reduction in the rate of severe exacerbations from 0.30 to 0.185. The conservative baseline rate of severe exacerbations per patient per year of 0.30 is derived from RCTs which have reported a rate of 0.21 in steroid-naïve subjects treated with budesonide 200µg/day, (using the same criteria for severe exacerbations, peak flow criteria excluded)[21] and rates in subjects previously treated with ICS at baseline of 0.92 and 0.96 (budesonide 200 and 400µg/day),[21] 0.35 (budesonide 800µg/day),[22] and 0.35 (budesonide 400µg/day).[23] Past research shows a relative risk (RR) of severe exacerbations of budesonide/ formoterol reliever therapy compared with SABA reliever therapy of between 0.52 and 0.55,[23,49] and a non-significant 38% reduction in severe exacerbations with ICS and SABA reliever therapy (separate inhalers) vs physician-adjusted maintenance ICS.[48] This 38% reduction in severe exacerbations[48] would be expected to be less than that observed in the proposed study, due to their study of highly compliant patients, the use of separate inhalers rather than a combination inhaler, and ICS/SABA rather than ICS/LABA reliever therapy. These estimates are directly relevant to this proposed study, and for the purpose of this power calculation, we plan to detect a conservative relative rate of severe exacerbations per patient per year of 0.62 with the ICS/LABA reliever regimen.

The primary outcome variable for the sub-study is the mean ICS dose per day. Assuming a drop-out rate of 10%, 110 patients will be recruited into the sub-study to ensure a sample size of 50 completed patients in each treatment arm, resulting in 90% power, alpha 5% to detect a 18% decrease in ICS use (µg/day) with ICS/LABA reliever therapy, compared with 264 µg/day in the standard ICS and SABA regimen. This calculation is based on data from our previous study of ICS compliance in stable asthma in which participants took a mean (SD) 66% (27) of their prescribed ICS dose.[37]

Timeframe: The recruitment of 890 subjects will occur over 30 months, similar to the recruitment rate in the SMART study of 300 subjects over 15 months.[2] This is achievable as there is an estimated six times more patients eligible for inclusion in this RCT compared with the SMART study.[2]

Sample size re-estimation at the blinded interim analysis point

We plan a blinded re-estimation of the required sample size for the trial at the interim analysis point. The currently planned blinded interim analysis of hospitalisations for asthma, after recruitment of about half the participants, aims to detect a safety signal that might require a Data Safety and Monitoring Committee review (see Section 13). We plan to also use this opportunity to carry out a blinded re-estimation of the sample size based on the rate of severe exacerbations in each of the arms of the study, masked as to treatment allocation. The current sample size was based on ~~a~~ an assumed rate in the ICS and as required SABA arm of 0.30 severe exacerbations per person per year, with 90% power to detect a rate of 0.185 events per person per year in the prn budesonide/formoterol arm, a relative rate of 0.62. In the blinded assessment of rate of severe exacerbations in the two treatment arms, if the higher of these two event rates is less than 0.30 events per year, then the sample size requirements will be larger than currently planned. The sample size will be estimated by simulation from appropriate Poisson distributions.

If the blinded sample size re-estimation shows that a considerable increase in recruitment would be required, the study team will consider whether the increase is reasonably achievable. If the team considers that the increased sample size is not achievable, a blinded sample size estimation using an outcome of 'asthma exacerbations per patient per year' will be performed. The team will then consider options such as changing the primary outcome variable from 'severe asthma exacerbations per patient per year' to 'asthma exacerbations per patient per year' (see definitions on page 7). Any change will be made prior to database lock.

11. Statistical analysis

11.1 Overall study outcomes

Primary outcome variable analysis

This will be an 'intention to treat' superiority analysis. The primary analysis of the primary outcome variable is comparison of the rate of severe exacerbations per patient per year until completion of the study or withdrawal from the study. This will be by Poisson regression with an offset for the time of observation. Over-dispersion will be evaluated prior to analysis and a corrected analysis applied if necessary.[2]

A sensitivity analysis will include the following potentially important predictors of response including age, sex, ethnicity, smoking status, baseline ACQ-5 score, severe exacerbation in the previous year, baseline ICS use, baseline FeNO, and baseline blood eosinophil count. This will account for different distributions of these variables in the treatment groups and increase precision of the estimates of differences. If the outcome data are sparse it may not be possible to include all of the confounding variables for the sensitivity analysis.

A separate sensitivity analysis will be performed using the definition of a severe exacerbation that has been used in the NovelSTART[68] study; i.e.: "prescription of corticosteroids for 3 or more days", irrespective of self-reported use.

Secondary outcome variable analyses

The following methods will be used:

Survival analysis illustrated by Kaplan-Meier plots and use of Cox proportional hazards regression to estimate the hazard ratio in relation to the randomised treatment:

- Time to first severe exacerbation [9.1.2.1.2]
- Time to first exacerbation [9.1.2.1.3]

Simple t-tests by time of measurement and mixed linear models for repeated measures by time:

- ACQ-5 score [9.1.2.1.6]
- FEV_1 [9.1.2.1.7]
- FEV_1 percentage predicted [9.1.2.1.8]
  FeNO, likely on the logarithm transformed scale based on our previous experience with the skewed distribution of this variable and that normality assumptions were better met on the logarithm transformed scale [9.1.2.1.9]

Comparison of proportions by logistic regression:

- The proportion of severe exacerbations defined by each criteria [9.1.2.1.4]
- The proportion of participants with at least one severe exacerbation [9.1.2.1.5]
- The proportion of participants withdrawn and reason [9.1.2.1.10]
- Adverse events [9.1.2.2.1]
- Serious adverse events [9.1.2.2.2]

Other:

- The WPAI:Asthma [9.1.2.3.2] consists of four sub-scores and t-tests will be used to compare each sub-score by randomised treatment if normality assumptions are met and the Mann-Whitney test if they are not.
- Beliefs about Medicines Questionnaire [9.1.2.4.1] consists of four sub-scores (Specific Necessity, Specific Concerns, General Overuse and General Harm).We plan to use t-tests comparing each sub-score by randomised treatment if normality assumptions are met and the Mann-Whitney test if they are not.
- Estimation of costs will be analysed by simple t-test [9.1.2.3.1].
- An exploratory descriptive analysis will be performed for the Participant attitudes, preferences and reliever use questionnaire [9.1.2.4.1]
- The analysis of the discrete choice experiment will be detailed in a separate statistical analysis plan [9.1.2.4.1].

11.2 Electronic monitoring sub-study outcomes

Primary outcome variable analysis

This will be an 'intention to treat' superiority analysis. The primary analysis of the primary outcome variable of mean ICS dose per day [9.2.1] will be by Poisson regression with an offset for the time of observation. Over-dispersion will be evaluated prior to analysis and a corrected analysis applied if necessary.[2] A sensitivity analysis will be performed as per the main study.

Secondary outcome variable analyses

Comparison of proportions by logistic regression:

- The proportion of participants with at least one day of no ICS actuations [9.2.2.1]
- The proportion of participants with at least one episode of high use [9.2.2.7.1]
- The proportion of participants with at least one episode of marked overuse [9.2.2.8.1]
- The proportion of high use episodes without medical review within 48 hours, 7 days and 14 days.[9.2.2.7.5]
- The proportion of marked use episodes without medical review within 48 hours, 7 days and 14 days.[9.2.2.8.5]

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

- Number of days of no ICS use [9.2.2.2]
- Number of ≥7 consecutive day periods of no ICS use [9.2.2.3]
- Number of ≥14 consecutive day periods of no ICS use [9.2.2.4]
- Number of days of high beta agonist use [9.2.2.7.2]
- Number of days of high beta agonist use in participants with at least one day of high beta agonist use [9.2.2.7.3]
- Number of high beta agonist use episodes without medical review in the following 48 hour, 7 day and 14 day periods in participants who had at least one high beta agonist use episode [9.2.2.7.4]
- Number of days of marked beta agonist overuse [9.2.2.8.2]
- Number of days of marked beta agonist overuse in participants with at least one day of marked beta agonist overuse [9.2.2.8.3]

- Number of marked beta agonist overuse episodes without medical review in the following 48 hour, 7 day and 14 day periods in participants who had at least one marked beta agonist overuse episode [9.2.2.8.4]

Descriptive data:

- Use of study medications in the 14 days prior to severe exacerbations [9.2.2.10]

Other:

- Total oral corticosteroid use, likely on the logarithm transformed scale based on our previous experience with the skewed distribution of this variable and that normality assumptions were better met on this scale [9.2.2.6.1]. This variable should be analysed by simple t-test, however may need to analysed by a Mann-Whitney test and Hodges-Lehmann estimator of location shift should many participants receive no oral corticosteroid. Similarly, composite corticosteroid use per year is likely to be on a logarithm transformed scale [9.2.2.6.3].
- For the longest duration of no ICS use (days) [9.2.2.5] and the maximum number of beta agonist actuations in a 24 hour period [9.2.2.9], the data distribution of will be examined for the likely most appropriate analysis strategy. If these are best treated as a count variable then Poisson regression will be used.
- The dataset will also be used to test the hypothesis that prolonged periods of non-ICS use (≥7 consecutive days, ≥14 consecutive days) have different associations with the probability of poor asthma control (end of study ACQ-5 score ≥1.5) or a severe exacerbation. Logistic regression with a non-ICS use-treatment interaction term will be used for severe exacerbations; ANCOVA, with a similar interaction term will be used for the ACQ-5 score.
- Analysis of the relative rates of high and marked beta agonist overuse without subsequent medical review within 48 hours, seven days and 14 days will be analysed by Poisson regression with an offset for the adjusted days of treatment exposure. If the analysis suggests over-dispersion and a dispersion term will be used to adjust for it.
- Comparison of blood eosinophils between the groups at visit 6, adjusted for baseline eosinophil count, with baseline ICS use as a covariate. [9.2.2.11]

11.3 Sub-group analysis

Sub-group analyses will be performed for two outcome variables: rate of severe exacerbations and ACQ-5. In these sub-group analyses the differential effect of treatment on outcome will be explored with each of the following potential moderating variables:

- SABA use at baseline, measured as the average number of occasions per week of self-reported SABA use in the four weeks before enrolment
- ICS use at baseline as a dichotomous variable as used or not used
- ICS adherence at baseline in those using ICS at baseline, with adherence measured both as proportion of self-reported adherence and as a dichotomous variable as adherence greater than 80% compared to a lesser amount
- Whether there has been a severe exacerbation in the year prior to enrolment
- Age at baseline
- Sex
- Ethnicity
- Smoking status at baseline

- Inhaler technique during the study defined as either satisfactory (when for ≥50% of attended scheduled study visits (Visit 2, 3, 4, 5, 6) the participant demonstrated satisfactory turbuhaler technique) or not (see Appendix Figure 6)
- Baseline ACQ-5 score (for severe exacerbation outcome only)
- Baseline FEV1 % predicted
- Baseline FeNO, Periostin and Baseline blood eosinophil count
- Baseline housing status
- Baseline NZ Deprivation Index score
- Baseline education status

Whether there is evidence of a sub-group effect will be tested by fitting interaction terms between treatment and the possible moderating variables for the two selected outcome variables. For the rate of severe exacerbations we plan to use Poisson regression, with an offset for the time of observation. Dependent on the data distribution for the severe exacerbations this may be better modelled as logistic regression if there are very few severe adverse events. ACQ-5 will be modelled with ANCOVA.

If the primary outcome variable is changed to 'rate of asthma exacerbations per patient per year' after the sample size re-estimation then this variable will be used in place of 'rate of severe exacerbations' for the sub-group analyses.

11.4 Economic analysis

Additional socioeconomic analyses will be undertaken, with a specific statistical analysis plan developed prior to completion of the study.

11.5 Ethnicity analysis

Additional analyses will be undertaken under the supervision of Dr Matire Harwood to explore differences in outcome according to ethnicity, in particular looking at outcomes of participants identifying as Maori or Pacific ethnicities. This analysis will be defined in an additional analysis plan but is expected to include a subgroup analysis comparing treatment response by ethnicity and exploration of differences in socioeconomic conditions, which may represent important confounding variables.

11.6 Periostin and future unspecified research analyses

Serum periostin and the additional optional future unspecified research samples for the analysis of novel biomarkers will be collected at baseline from a sub-set of up to 150 participants, recruited at the MRINZ only. These samples will be analysed according to a separate analysis plan, to be developed prior to completion of the study. Biomarkers to be analysed will be determined based on the results of a separate piece of research currently ongoing into biomarkers of Th2 responsiveness in asthma.

11.7 Electronic monitoring analysis

An interim analysis to assess the number of participants recruited to the study taking inhaled corticosteroids at baseline will be undertaken at the point that the 33rd patient is recruited to the sub-study. If fewer than 25% of participants (ie, 8 participants) are found to be inhaled corticosteroid naïve at baseline, then a process of preferentially recruiting this group will be undertaken with the aim of achieving a minimum of 25% steroid naïve at baseline and ideally between 33% and 50%. If 25% are steroid naïve at baseline, using the same assumptions

as for the main power calculation, there will be 80% power to detect a difference in outcome according to baseline ICS use. If 33% are steroid naïve at baseline this increases to 90%.

In the final analysis, absolute values and percentages will be presented for:

- Total number of monitors dispensed, and with which medication
- Number of monitors that failed pre study checks
  - Why (extra actuations, missed actuations, battery, failure to upload data, other)
- Number of monitors that failed within study checks
  - Why (extra actuations, missed actuations, battery, failure to upload data, other)
- Ability to upload data from failed monitors by Adherium
- Number of monitors lost/thrown away by participants
- Overall number of monitors supplying complete data without loss or failed within study checks

11.8 Combined analysis of PRACTICAL and Novel START trials

Standardisation of key features of the protocols will enable a combined analysis of individual patient data from the PRACTICAL and Novel START trials.[68] For this analysis, data will be combined for the comparison of the ICS/LABA reliever therapy and ICS maintenance and SABA reliever therapy regimens, with the rate of severe exacerbations per patient per year the primary outcome variable.

The PRACTICAL and NovelSTART studies have a different definition of a severe asthma exacerbation. The PRACTICAL study uses a definition based on “use of systemic corticosteroid for at least 3 days because of asthma”, determined through self-reported corticosteroid use. Whereas, the definition used in the NovelSTART study is based on “prescription of systemic corticosteroids for 3 or more days”, and self-reported use is not taken into account. This is because participants are withdrawn from NovelSTART at the point of steroid prescription and as a study with a SABA monotherapy arm it was considered unsafe to allow people requiring a prescription of corticosteroids for a severe asthma exacerbation to continue in the study, irrespective of subsequent self-reported use.

The primary combined analysis will be an ‘intention to treat’ superiority analysis. The primary analysis of the primary outcome variable is comparison of the rate of severe exacerbations per patient per year until completion of the study or withdrawal from the study. The PRACTICAL definition of a severe asthma exacerbation will be used for this analysis. This will be by Poisson regression with an offset for the time of observation. Over-dispersion will be evaluated prior to analysis and a corrected analysis applied if necessary.[2]

A sensitivity analysis will include the following potentially important predictors of response including age, sex, ethnicity, smoking status, baseline ACQ-5 score, severe exacerbation in the previous year, baseline ICS use, baseline FeNO, and baseline blood eosinophil count. This will account for different distributions of these variables in the treatment groups and to increase precision of the estimates of differences. If the outcome data are sparse it may not be possible to include all of the confounding variables for the sensitivity analysis.

A separate sensitivity analysis will be performed on the combined dataset using the NovelSTART definition of a severe exacerbation, i.e.: “prescription of corticosteroids for 3 or more days”, irrespective of self-reported use.

12. Electronic monitoring, for participants allocated for electronic monitoring only

12.1 Monitor kits

12.1.1 Participants will be allocated electronic monitors by the investigator, in accordance with Section 7 and a separate study manual.

12.1.2 Electronic monitors (Adherium) with unique ID numbers are to be attached to each inhaler to record the date and time of every actuation, and to allow a detailed assessment of the patterns of use of the randomised treatments.

12.1.3 Should an investigator incorrectly allocate an electronic monitor to a participant, contact must be made with the Sponsor as soon as possible.

12.2 Monitors

12.2.1 Will record the date and time of inhaler actuations.

12.2.2 Will have individual ID numbers and will remain participant-specific during the course of the study.

12.2.3 Will upload data via USB at the study visit via software provided by Adherium.

12.2.4 Participants using monitors will be told that they are using a modified inhaler that has been produced specifically for this sub-study to count the precise number and timing of doses used during the study period. This will provide a reason for the need to avoid using other inhalers. Participants will be told that the purpose of the sub-study is to compare the benefits of the two treatment regimens and to determine whether the patterns of use influence outcome

12.3 SmartInhalerLive website

12.3.1 Data will be uploaded to the website.

12.3.2 Investigators are to check that data has been uploaded successfully.

12.3.3 Investigators should not investigate the participant's daily patterns of inhaler use over the study period or discuss any uploaded data with the participant, as this may change Investigator and patient behaviour, influencing study outcomes.

12.4 Pre-site, pre-dispensing and collection checks

12.4.1 A comprehensive trial quality control programme will be implemented for all monitors and involves testing prior to dispensing and during the full study period, as performed in our previous RCT.[69,70] This will be detailed in separate study documentation.

12.5 Monitor data analysis

12.5.1 Electronic data on days of study visits will be discounted in the analysis, because dose dumping may occur at this time as well as validation testing of inhalers.

12.5.2 Data that meets dose dumping criteria will be discounted by the investigator checking the website. Dose dumping is defined as greater than or equal to 100 actuations in a three hour period.

13. Safety monitoring, adverse events and serious adverse events

A DSMC will be established chaired by Dr Rodolfo Morice, Respiratory Senior Medical Officer, Wellington Hospital , who is independent from the study team. The DSMC will review all serious adverse events and the results of the interim safety statistical analysis undertaken when 500 patients have been randomised. The interim safety statistical analysis will be conducted by the study statistician, Prof Mark Weatherall, for all unplanned hospitalisations for asthma. This analysis will be performed masked to treatment allocation (the trends for analysis will be provided without the patient ID code, but with the blinded randomised treatment code (e.g. treatment 1 or treatment 2)). The calculated interim P value for performing a safety review of the study (using the 1d98 Program), is 0.006 (using a one-sided O'Brien-Fleming boundary). The proportion of participants with an unplanned hospitalisation for asthma will be compared to the expected proportion of 2.0% using the binomial test for proportions. If the observed rate exceeds the expected rate with a P value <0.006, a safety review of the study will be undertaken. The P value calculations use the 1d98 Program, an alpha spending function, with alpha nominated as 0.05, evenly distributed analysis times, and O'Brien Fleming boundaries. The expected proportion is half that observed in the recent study of patients with more severe asthma.[2] If the findings of the safety analysis indicate a safety review is necessary, then termination of the trial will be considered.

The DSMC will review protocol deviations and withdrawals for pooled data and have the capacity to request an analysis with masked treatment code for any variable amongst the treatment arms.

Unblinded data can be made available at the DSMCs request.

13.1 Adverse events (AEs)

An adverse event is any untoward medical occurrence in a study subject temporally associated with participation in the trial and the administration of study medication, whether or not considered related to the medicine. An adverse event can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of the study treatment. A worsening of a pre-existing medical condition other than asthma will be considered an adverse event. For detail on worsening of asthma see Section 13.3.

Adverse event data will be collected and analysed with efficacy data at the end of the study. If an adverse event is ongoing at the last visit, this will be followed up as required by the investigator, but will not require recording in the eCRF. The Sponsor may request further follow-up data on adverse events, if necessary. Serious adverse events will be notified to the sponsor and the internal data safety monitoring committee within 24 hours of investigators becoming aware of them.

Participants will be asked to grade adverse events and the maximum severity will be recorded in the eCRF, according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated).
- Moderate (discomfort sufficient to cause interference with normal activities).

- Severe (incapacitating, with inability to perform normal activities).

It is noted that there is a distinction between serious and severe AEs. Severity is a measure of intensity, as outlined above, whereas seriousness is defined by the criteria in Section 13.2.

An assessment of causality and expectedness will be performed by the Investigator submitting the adverse event report. Causality will be based on the Investigator's judgement and will result in a decision of related, or not related, to Study Drug.
Causality will be assessed based on:

- Related: The temporal relationship of the AE or SAE to Study Drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.

- Unrelated: The temporal relationship of the AE or SAE to Study Drug administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide sufficient explanation for the AE/SAE.

Expectedness will be assessed against the Medsafe Data sheet for each Study Drug.

Adverse events or adverse drug reactions shall be reported to relevant health authorities in accordance with applicable laws, and to the New Zealand Health and Disability Ethics Committee in accordance with its policies.

13.2 Serious adverse events (SAEs)

For the purposes of this study the following events will be considered to be SAEs and require expedited reporting:

- Death.

- Life-threatening event.

- Permanently disabling or incapacitating event.

- Hospitalisation or prolongation of hospitalisation. Hospitalisation for the purposes of SAE reporting is defined as an admission to hospital and does not include a presentation to the ED followed by discharge without admission or an admission for elective reasons.

- A congenital abnormality or birth defect.

- Any event considered serious by the study investigator.

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 may request further follow-up data on SAEs, if necessary.

If the eCRF is not available, an SAE report should be faxed to the Sponsor within 24 hours, to +64-4-389 5707.

The Sponsor will receive notification of SAE submission via the eCRF and will review SAEs on an ongoing basis, within 1 working calendar day (based on NZ time) of submission by the Investigator. An assessment will be made by the Sponsor as to the causality and expectedness of the event, based on the Investigator's report and the relevant Data Sheet.

13.3 Pregnancy and/or breastfeeding

Females pregnant, breastfeeding or planning pregnancy at the time of recruitment will be excluded from participating in the trial. Should a female subject enrolled on the study become pregnant during the course of the trial she should inform investigators at her earliest opportunity and be withdrawn from the study. Current clinical practice allows for the use of budesonide or combination budesonide/formoterol during pregnancy, as the benefits to both mother and child of adequate asthma control outweigh the theoretical risks of treatment. The subject will be asked to contact the researchers after the birth of the baby and any congenital anomaly or birth defect will be considered to be an SAE.

13.4 Asthma exacerbations

If a study participant has an exacerbation during the study, they will be asked to contact their GP for assessment and management or visit an ED/Clinic in accordance with their action plan. It will be reinforced to the study participants that they will receive standard medical care (from their GP, after hours or ED) for their asthma during the course of the study.

- Subjects randomised to budesonide/formoterol for relief will be advised that should they take more than 8 inhalations of budesonide/formoterol over any 24 hour period they should see their doctor or attend ED the same day.

- Subjects randomised to budesonide for maintenance and terbutaline for relief will be advised that should they take more than 16 inhalations of terbutaline over any 24 hour period they should see their doctor or attend ED the same day.

As per the action plans, if participants usually measure their own peak flow at home they should continue to do this and seek medical review should this drop to below 60% of best measurement.

The comparative efficacy of the medication regimens on asthma control is an objective of this study. Worsening asthma resulting in urgent medical review (primary care visit, ED visit or hospital admission) and/or use of systemic corticosteroids, such as a course of oral prednisone for any duration will be reported as adverse events (or SAEs, if applicable) and will also be reported on the severe asthma exacerbation log within the eCRF. Should a participant report a worsening of asthma that does not meet the criteria for an exacerbation (e.g. feeling more wheezy than usual, worse ACQ score), this will be considered part of the fluctuating course of asthma, and not to be an AE.

13.5 Monitoring

The Sponsor will monitor the study in accordance with Good Clinical Practice guidelines and the Study Monitoring Plan. A Sponsor representative, the Clinical Trial Monitor, will have regular contact with the sites and will act as the first point of contact during the study. The Clinical Trial Monitor will perform on-site monitoring visits at specified intervals to include the following:

- Site performance assessment, to confirm recruitment rates, protocol adherence and study drug accountability.

- Perform source data verification activities (e.g. verify the severe exacerbation data entered into eCRF against the source data for each subject, as per the Study Monitoring Plan).

- Provide advice/ support as necessary for the site.

Remote monitoring of data will also take place, to ensure any logical inconsistencies or missing data can be resolved prior to the on-site monitoring visit, and throughout the study. The eCRF will also provide inbuilt validation checks to ensure consistent and correct data are entered.

A close-out visit will also be performed once the study has completed, to formally close out each site and to ensure any ongoing responsibilities are met.

14. Electronic data capture

An eCRF will be used to randomise subjects into the study, dispense and track medications and enable data entry for each patient. After they have received training, study staff will be given appropriate access to the eCRF system and will complete subject study data entry on an ongoing and timely basis within the system. The eCRF system will be separate from the site specific collection of individual subject medication use (via the electronic monitors), which will take place as outlined in Section 12.

The Participant attitudes, preferences, and reliever use questionnaire will be administered via REDCap. REDCap is a secure, 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; and 4) procedures for importing data from external sources.
After they have received training, study staff will be given appropriate access to the REDCap system, for administration of the questionnaire. The completion of the questionnaire will be performed by the participant.

The Discrete Choice Experiment will be administered via 1000minds online portal; https://www.1000minds.com/. No identifiable data will be entered into the portal and the final dataset will be exported from the portal and stored long term on MRINZ controlled servers. The completion of the questionnaire will be performed by the participant.

15. Site training

Site initiation visits will be held at each site.
Site initiation visits will be performed by the Sponsor representatives, including the Clinical Trial Monitor. These will ensure the site is ready to begin recruiting for the study and that all necessary approvals (ethics/regulatory/research office etc) are in place prior to the first patient enrolment, and to provide training on the eCRF and Electronic Monitors, as well as study specific procedures e.g. spirometry and the checking and training of inhaler technique. The appropriate manuals and guidelines will also be issued to sites in order that they are able to perform the study as per protocol. Any additional training for study procedures will be performed as necessary.

16. Ethics

16.1 Ethical considerations

All patients will be randomised to receive ICS. Participants deemed to be at 'high risk' will be excluded, on the basis of a previous ICU admission or if they have uncontrolled asthma despite satisfactory inhaler technique and ≥80% adherence to their prescribed ICS treatment prior to recruitment. Participants will be followed closely during the study with provision of asthma action plans. Investigators may choose to withdraw a study participant at any time due to safety concerns, including concerns that uncontrolled asthma requiring a step up in therapy. As a result, we are confident that all patients randomised in the study will be at substantially lower risk during the study than if they had not been enrolled.[72]

16.2 Ethics and regulatory review

The study does not require submission to Medsafe (via the Standing Committee on Therapeutic Trials), as the Study Drugs are approved products in New Zealand, being investigated in a slightly different population of patients, therefore the study is not under the scope of Medsafe review or the need for approval under Section 30 of the Medicines Act 1981.

Ethical Submission will be made to one of the Health and Disability Ethics Committees of New Zealand. The opinion of the Ethics Committee will be given in writing. Locality approval must be granted at each site before any participants are recruited, as per 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 Sponsor will provide the Principal Investigators with safety updates/reports from the study, including informing them of any updates to the Medsafe Datasheets.

16.3 Ethics and regulatory reporting

The Co-ordinating 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.
Local reporting requirements will be fulfilled by the Principal Investigator at each trial site, including submission of any required progress reports to their host institution.

The Sponsor will provide each Principal Investigator with safety updates/reports, including safety information relating to any serious and unexpected adverse drug reactions from this study.

16.4 Participant confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified by a randomisation ID number on study documents that are sent outside of the individual study site and on the inhaler monitor electronic database/ website. The eCRF will capture participant initials, date of birth, ethnicity, NHI number and address, as part of demographic information. All documents will be stored securely and only accessible by study staff (at site and Sponsor level) and authorised personnel.

Individual participant address is being captured centrally by the Medical Research of New Zealand (study Sponsor) so that New Zealand Deprivation Index data can be obtained from Statistics New Zealand. This is to enable the socioeconomic analyses to be performed, which include investigating the usefulness of Deprivation Index data to predict participant outcomes. The NHI number is being collected to enable validation of the primary outcome. It is recognised that provision of address and NHI number involves the sending of potentially identifiable data outside of the investigational site. This will be outlined specifically to the participant in the PIS-CF so that they are aware of this provision of their data and can provide their consent to its use in this way. The 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. The Sponsor will only use a participant's address and NHI number for the purposes outlined above. No study reports will contain any information that could individually identify a study participant.

Each site will comply with applicable data protection laws when recording and locally storing information for the study.

Data recorded in the eCRF and REDCap will be securely stored on servers in Australia.

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

Periostin samples will be analysed at:
Covance Central Laboratory
8211 SciCor Drive
Indianapolis, IN 46214
USA

Future unspecified research samples will be analysed at Genentech Inc. or a third party or affiliate working on their behalf and will be stored long-term in the RCR biobank.
All blood samples sent overseas for centralised analysis will be de-identified, with identifiable information such as participant name removed, and replaced with a unique identifier (i.e. coded).

The Sponsor will have access to and obtain all study data from the eCRF and inhaler monitor website and securely store it (electronically and in hard copy format as applicable) in New Zealand, at the Medical Research Institute of New Zealand.

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

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17. Finance and insurance

17.1 Funding

The primary funding is being provided by the Health Research Council of New Zealand, through a programme grant to the MRINZ. The funding agreement is made between the HRC and MRINZ, as Sponsor.

Funding for the collection materials, shipping and analysis of Periostin and future unspecified research samples will be provided by Genentech Inc. This funding agreement is made between Genentech and MRINZ, as Sponsor.

MRINZ will enter into contracts with study sites and will provide funding in the form of per-participant payments, paid for each completed visit (including data completion for that visit).

17.2 Participant reimbursement

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

17.3 Insurance

This study is not being conducted for the benefit of a drug manufacturer or distributor and therefore insurance to cover participant injury due to participation in the study is not required. Participants may claim under the Accident Compensation Act 2001 for injury sustained during the study, if appropriate. Insurance should be maintained each trial Site, as applicable to their requirements for conducting clinical research.

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18. 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.

19. References

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Appendix

RCT of an ICS/LABA reliever therapy regimen in asthma

Short title: PRACTICAL: PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist

UTN: U1111-1174-2273

Protocol Version: 4.0 (21 February 2018)

Protocol Number: MRINZ/15/A2

Figure 1: Study design

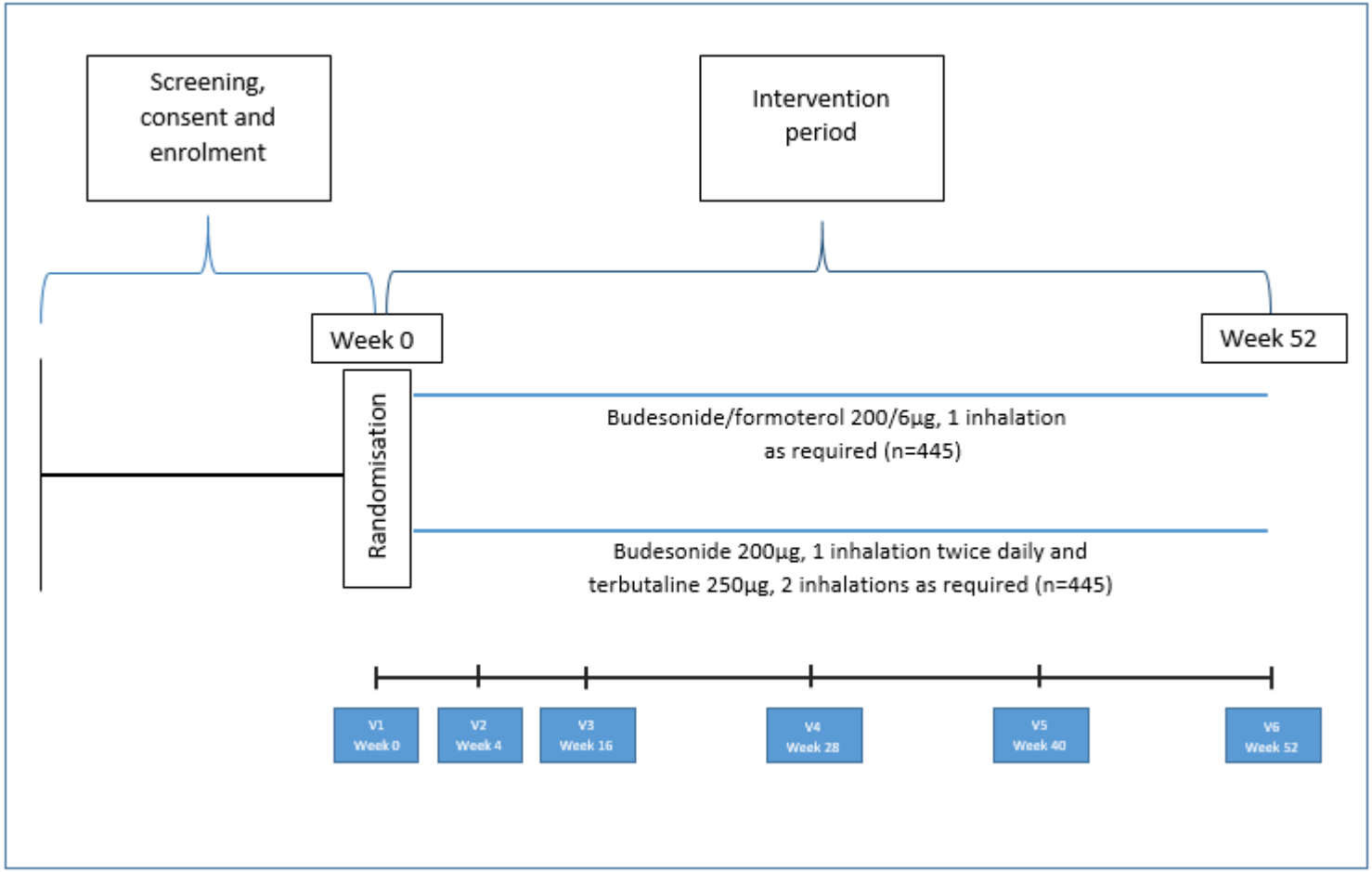


Figure 2: ICS & SABA self-management plan – front

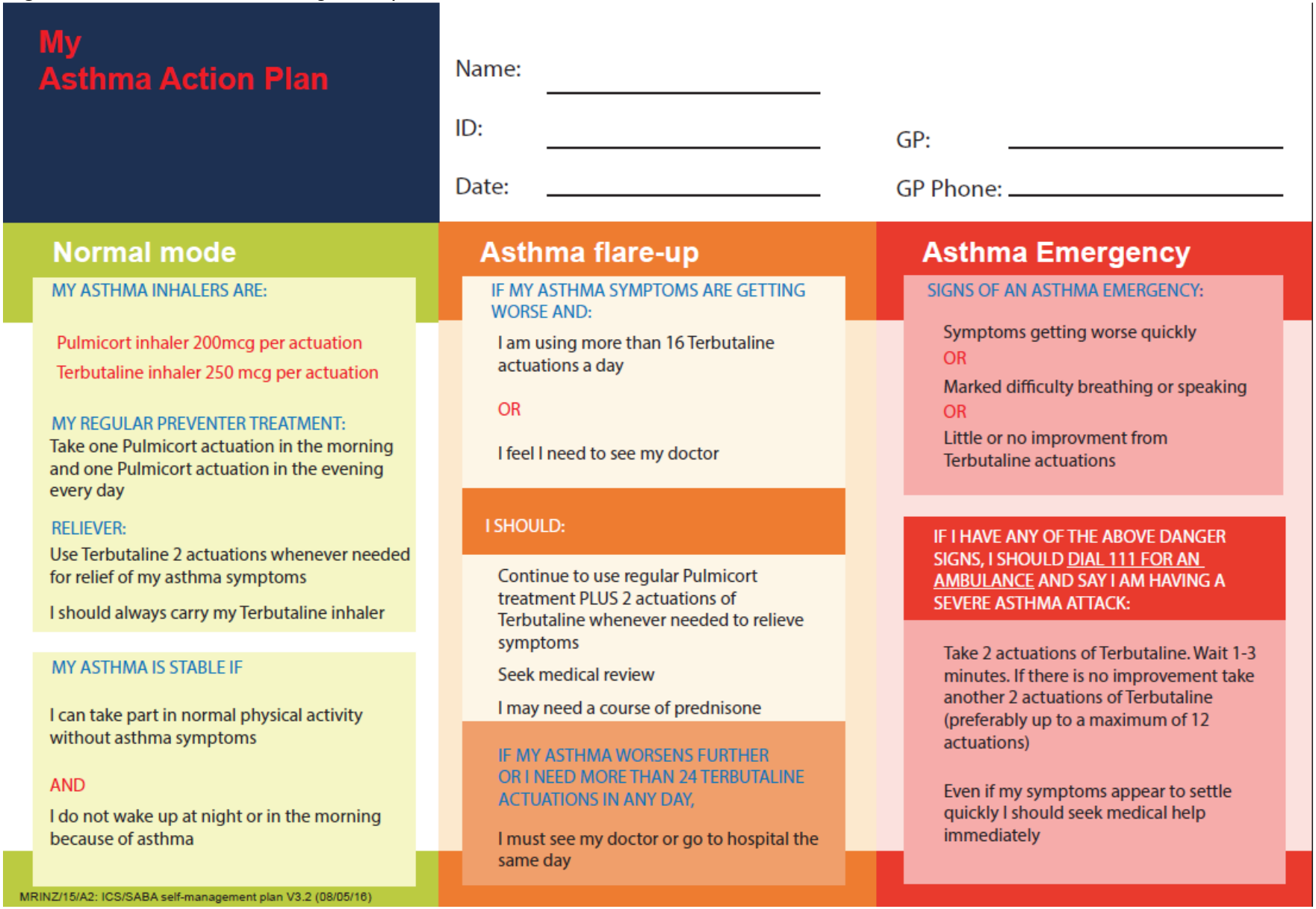
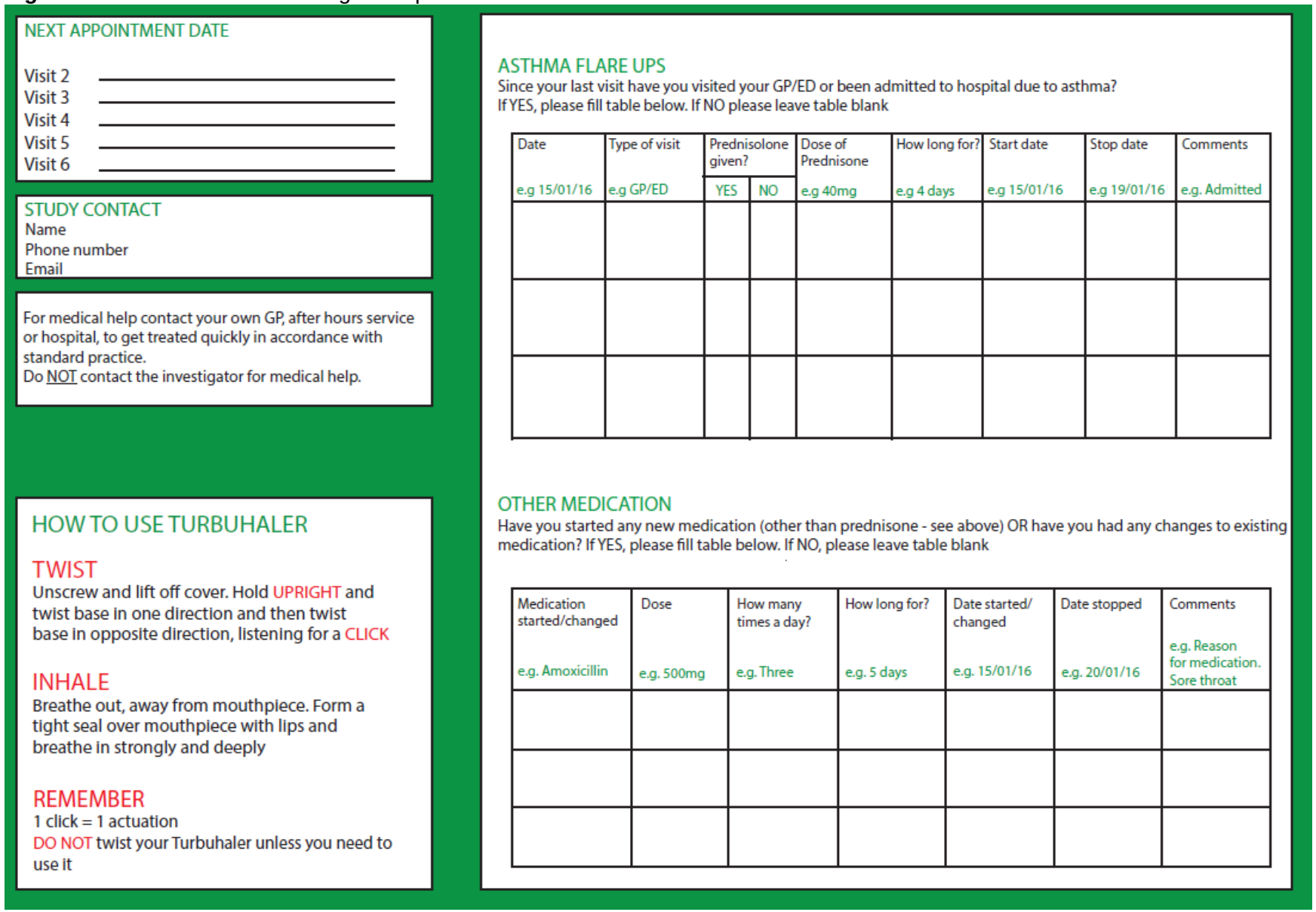


Figure 2.1: ICS & SABA self-management plan – back



NEXT APPOINTMENT DATE

Visit 2 _____
Visit 3 _____
Visit 4 _____
Visit 5 _____
Visit 6 _____

STUDY CONTACT
Name
Phone number
Email

For medical help contact your own GP, after hours service or hospital, to get treated quickly in accordance with standard practice.
Do NOT contact the investigator for medical help.

HOW TO USE TURBUHALER

TWIST
Unscrew and lift off cover. Hold UPRIGHT and twist base in one direction and then twist base in opposite direction, listening for a CLICK

INHALE
Breathe out, away from mouthpiece. Form a tight seal over mouthpiece with lips and breathe in strongly and deeply

REMEMBER
1 click = 1 actuation
DO NOT twist your Turbuhaler unless you need to use it

ASTHMA FLARE UPS
Since your last visit have you visited your GP/ED or been admitted to hospital due to asthma?
If YES, please fill table below. If NO please leave table blank

Date e.g 15/01/16	Type of visit e.g GP/ED	Prednisolone given? YES	 NO	Dose of Prednisone e.g 40mg	How long for? e.g 4 days	Start date e.g 15/01/16	Stop date e.g 19/01/16	Comments e.g. Admitted

OTHER MEDICATION
Have you started any new medication (other than prednisone - see above) OR have you had any changes to existing medication? If YES, please fill table below. If NO, please leave table blank

Medication started/changed e.g. Amoxicillin	Dose e.g. 500mg	How many times a day? e.g. Three	How long for? e.g. 5 days	Date started/ changed e.g. 15/01/16	Date stopped e.g. 20/01/16	Comments e.g. Reason for medication. Sore throat

Figure 3: ICS & SABA self-management plan with peak flow – front

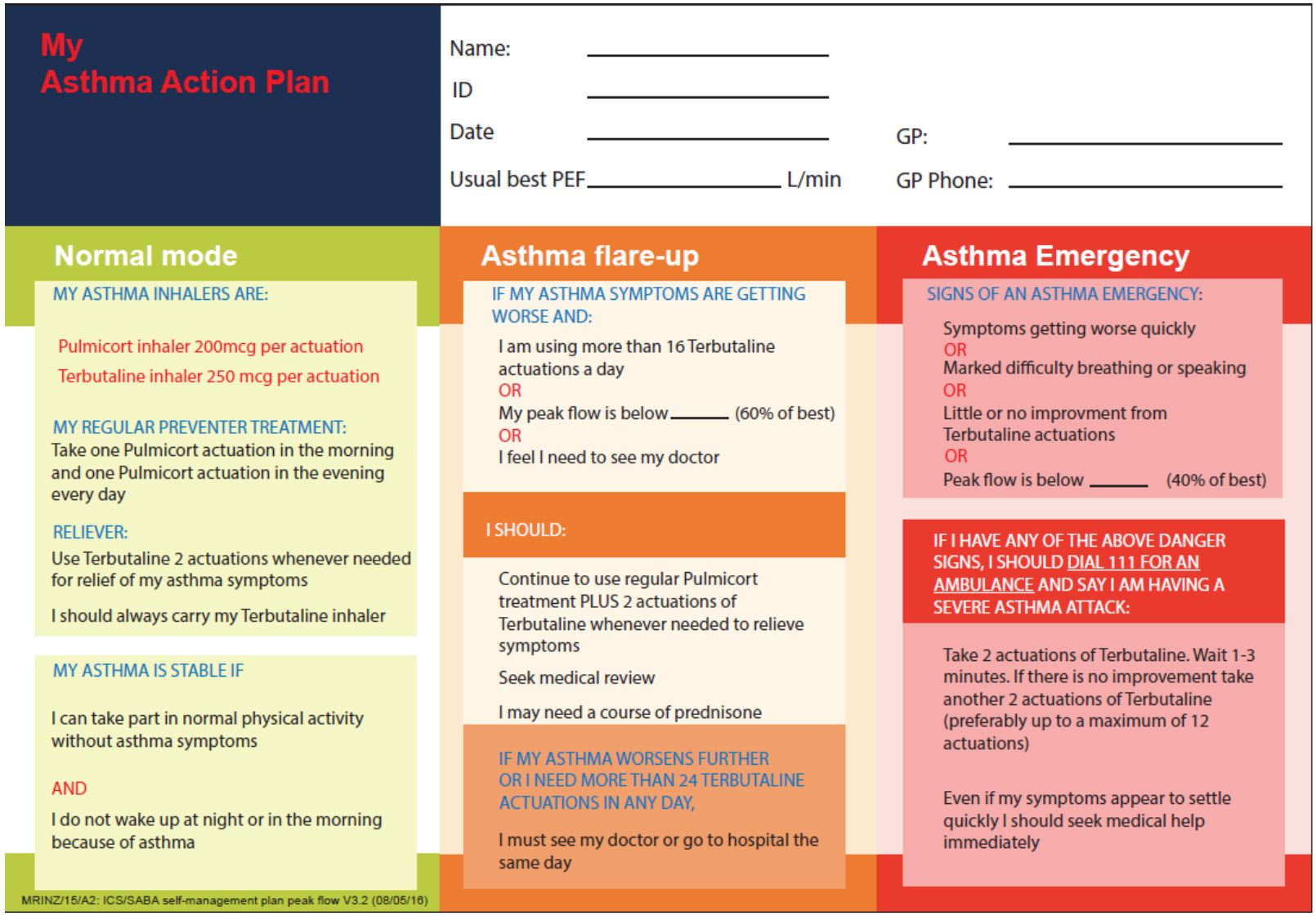
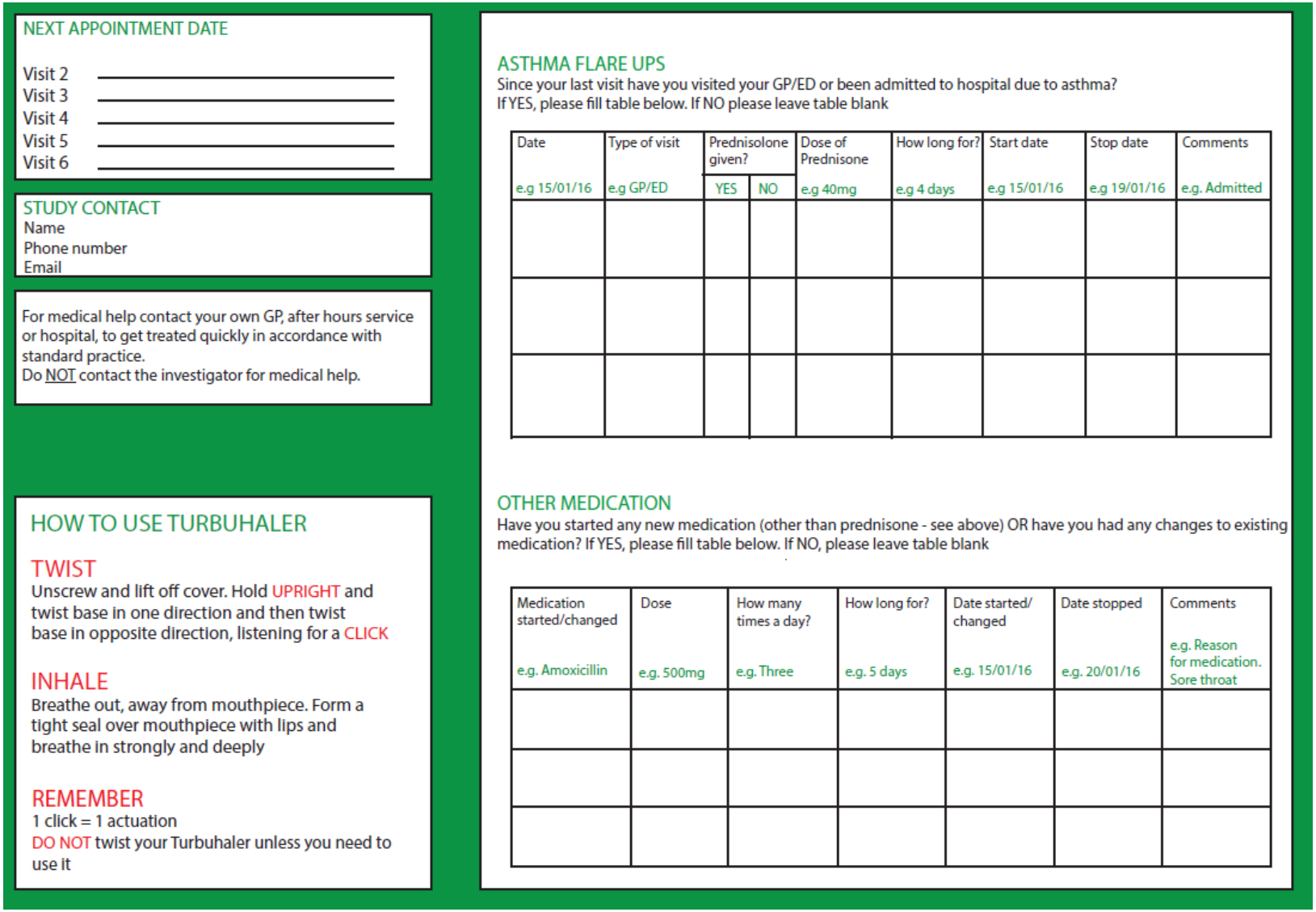


Figure 3.1: ICS & SABA self-management plan with peak flow – back



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Medication started/changed e.g. Amoxicillin	Dose e.g. 500mg	How many times a day? e.g. Three	How long for? e.g. 5 days	Date started/ changed e.g. 15/01/16	Date stopped e.g. 20/01/16	Comments e.g. Reason for medication. Sore throat

Figure 4: Symbicort self-management plan – front

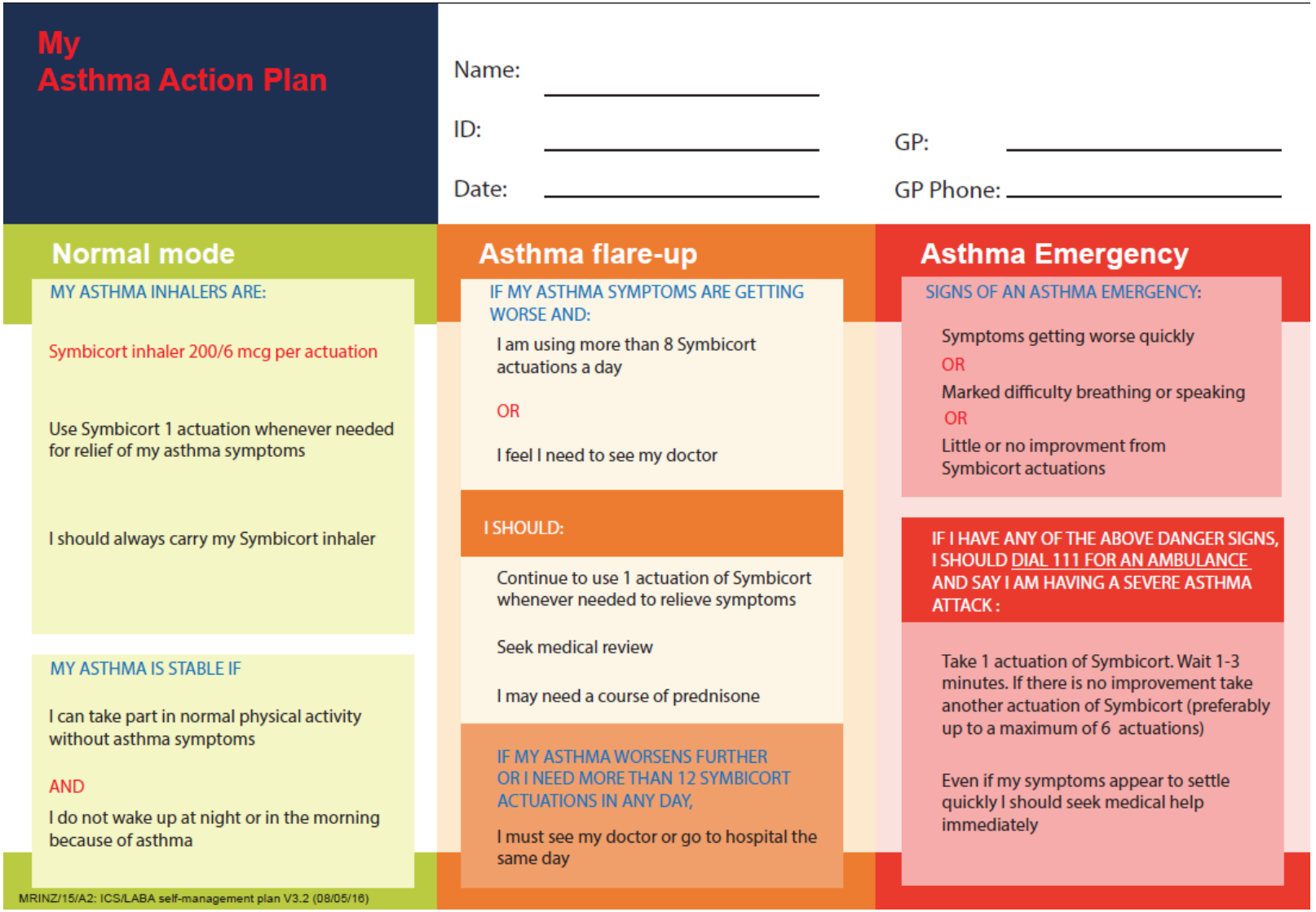
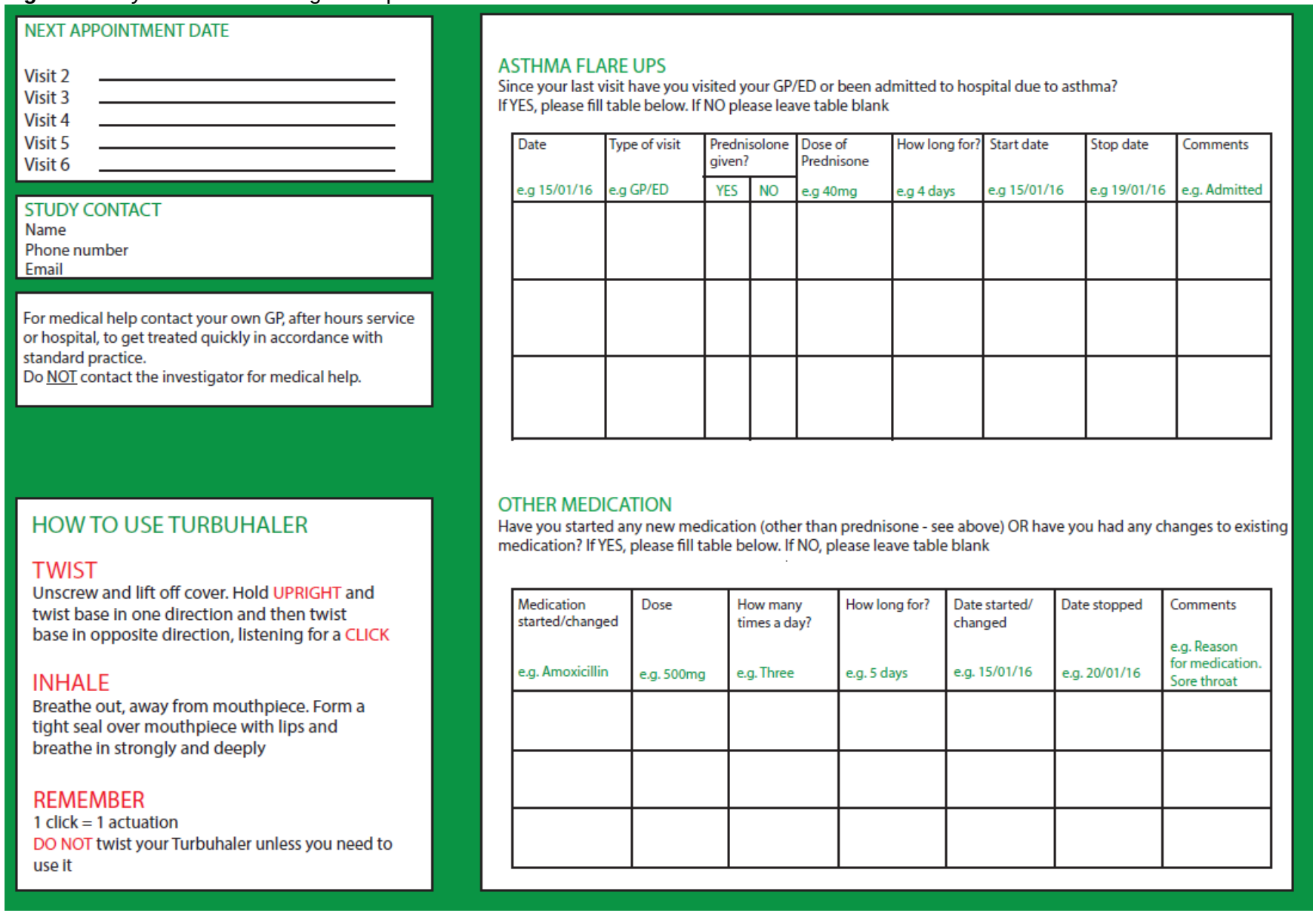


Figure 4.1: Symbicort self-management plan - back



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Date	Type of visit	Prednisolone given?		Dose of Prednisone	How long for?	Start date	Stop date	Comments
e.g 15/01/16	e.g GP/ED	YES	NO	e.g 40mg	e.g 4 days	e.g 15/01/16	e.g 19/01/16	e.g. Admitted

OTHER MEDICATION
Have you started any new medication (other than prednisone - see above) OR have you had any changes to existing medication? If YES, please fill table below. If NO, please leave table blank

Medication started/changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Comments
e.g. Amoxicillin	e.g. 500mg	e.g. Three	e.g. 5 days	e.g. 15/01/16	e.g. 20/01/16	e.g. Reason for medication. Sore throat

Figure 5: Symbicort self-management plan with peak flow – front

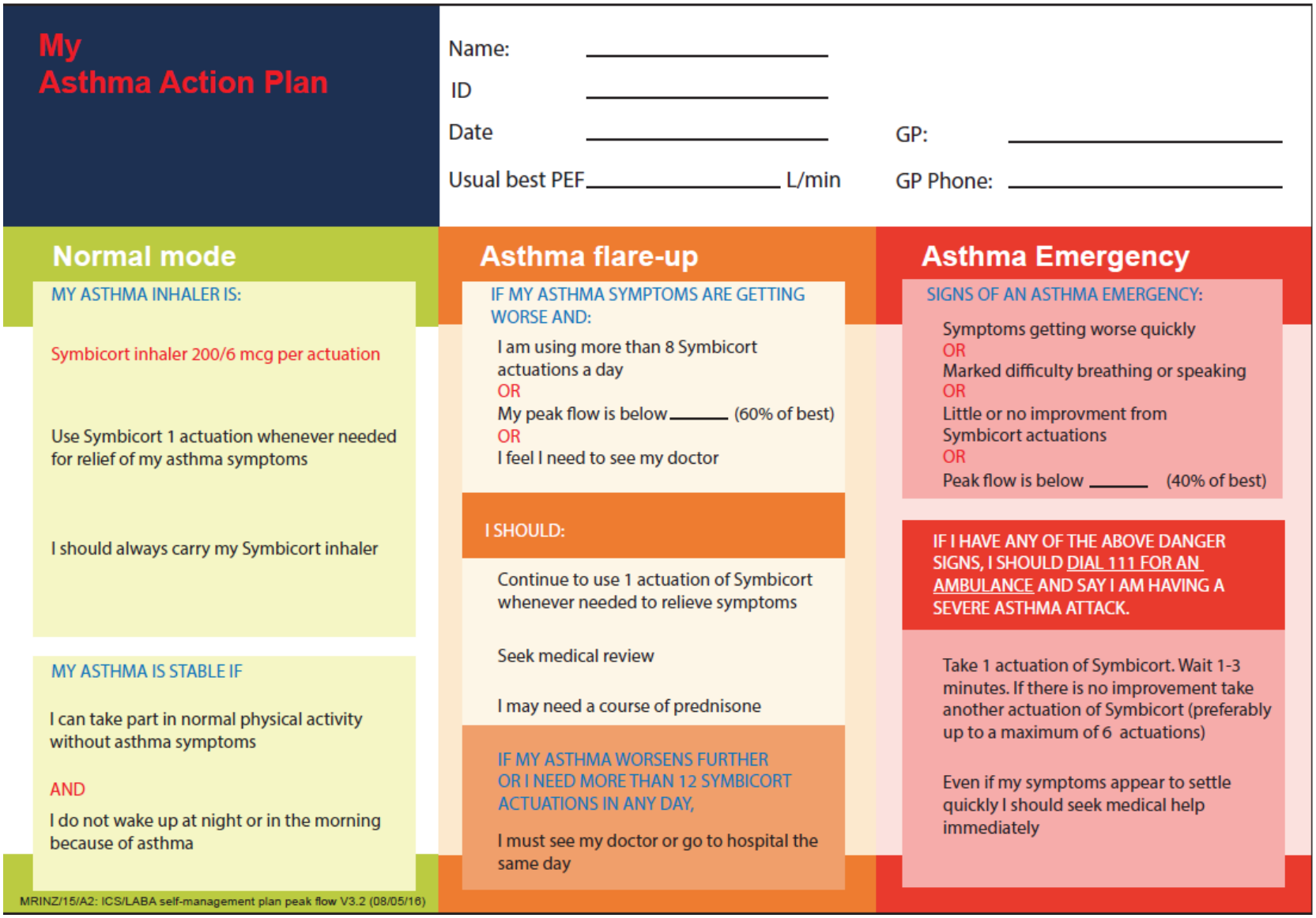
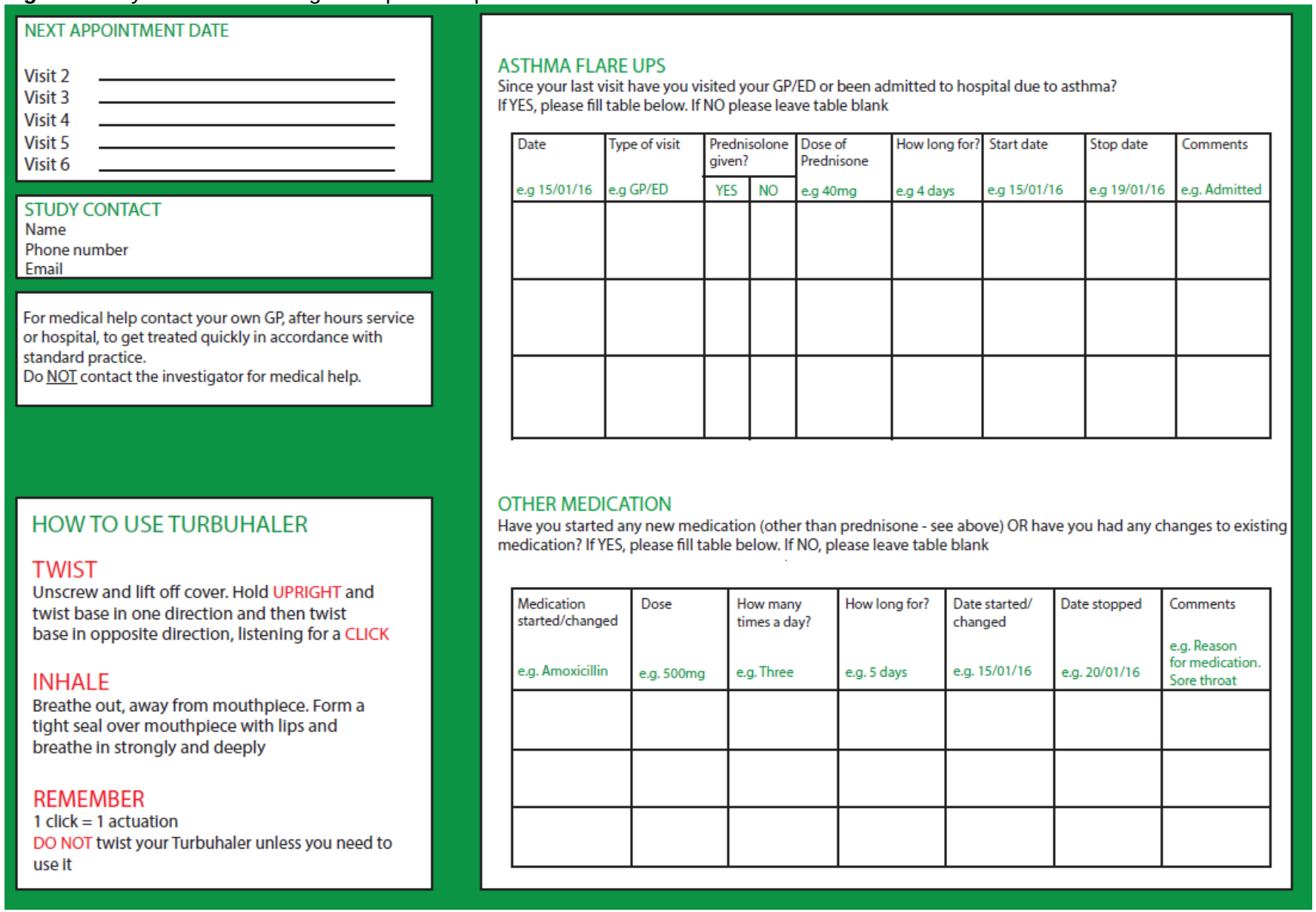


Figure 5.1: Symbicort self-management plan with peak flow – back



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Unscrew and lift off cover. Hold UPRIGHT and twist base in one direction and then twist base in opposite direction, listening for a CLICK

INHALE
Breathe out, away from mouthpiece. Form a tight seal over mouthpiece with lips and breathe in strongly and deeply

REMEMBER
1 click = 1 actuation
DO NOT twist your Turbuhaler unless you need to use it

ASTHMA FLARE UPS
Since your last visit have you visited your GP/ED or been admitted to hospital due to asthma?
If YES, please fill table below. If NO please leave table blank

Date e.g 15/01/16	Type of visit e.g GP/ED	Prednisolone given? YES	 NO	Dose of Prednisone e.g 40mg	How long for? e.g 4 days	Start date e.g 15/01/16	Stop date e.g 19/01/16	Comments e.g. Admitted

OTHER MEDICATION
Have you started any new medication (other than prednisone - see above) OR have you had any changes to existing medication? If YES, please fill table below. If NO, please leave table blank

Medication started/changed e.g. Amoxicillin	Dose e.g. 500mg	How many times a day? e.g. Three	How long for? e.g. 5 days	Date started/ changed e.g. 15/01/16	Date stopped e.g. 20/01/16	Comments e.g. Reason for medication. Sore throat

Figure 6: Asthma Inhaler Technique– Essential Steps for Eligibility Assessment

Unsatisfactory technique is defined as:

1. ANY of the essential steps listed below are NOT met, or

2. Overall technique not satisfactory for the delivery of medication, as deemed by overall investigator assessment

Assessment of technique:

1. **Technique with any ICS inhaler will be assessed prior to randomisation to assess eligibility.** Technique is ONLY to be assessed in participants who are using an ICS inhaler, and ONLY for the participant's ICS inhaler. *For example if the participant uses a Pulmicort Turbuhaler and salbutamol metered dose inhaler, they are assessed only on their Turbuhaler technique as part of the inclusion/exclusion check prior to randomisation*

TURBUHALER ESSENTIAL STEPS

- ☐ 1. Unscrew and remove cover
- ☐ 2. Keep inhaler upright while twisting grip
- ☐ 3. Twist around and then back until click is heard
- ☐ 4. Breathe in strongly and deeply

PRESSURISED METERED DOSE INHALER ESSENTIAL STEPS

(Note: Use of ICS pMDI without a spacer is classified as 'unsatisfactory technique' except for Authohaler, which cannot be used with a spacer. See below.)

- ☐ 1. Remove inhaler cap
- ☐ 2. Hold inhaler upright and shake well
- ☐ 3. Insert inhaler into spacer
- ☐ 4. Put mouthpiece between teeth without biting and close lips to form good seal
- ☐ 5. Hold spacer level and press down firmly on inhaler canister once
- ☐ 6. Breathe in slowly and deeply *(Note: tidal breathing method with ICS pMDI is classified as 'unsatisfactory technique')*

ACCUHALER

- ☐ 1. Open cover using thumb grip
- ☐ 2. Holding horizontally, load dose by sliding lever until it clicks
- ☐ 3. Breathe in steadily and deeply

AUTOHALER

- ☐ 1. Remove cap
- ☐ 2. Hold inhaler upright and shake well
- ☐ 3. Push lever up
- ☐ 4. Breathe in slowly and deeply. Keep breathing in after click is heard.

ELLIPTA

- ☐ 1. Slide the cover down until you hear a click (do not shake the inhaler)
- ☐ 2. Breathe in steadily and deeply

NOTE: These steps are based on the asthma inhaler technique device specific checklists by the National Asthma Council Australia (http://www.nationalasthma.org.au/health-professionals/primary-care-resources/asthma-inhaler-technique).

Figure 7: Asthma Inhaler Technique– On Study Essential Steps

Unsatisfactory technique is defined as:

1. ANY of the essential steps listed below are NOT met, or

2. Overall technique not satisfactory for the delivery of medication, as deemed by overall investigator assessment

Assessment of technique:

1. **Technique with study Turbuhalers at Visit 1:**
   To take place after randomisation and inhaler technique education, to confirm that the participant can use the study Turbuhalers correctly. This training will occur on supplied dummy Turbuhalers (NOT the participant's study medication). After training, label the participant's dummy inhaler with their name and study ID, and store it in a resealable plastic bag for use at their subsequent visits.

2. **Technique with study Turbuhalers at scheduled study Visits 2-6:**
   To take place PRIOR to participant education. For each participant, the same dummy inhaler can be used at each visit for checking their technique. At Visits 2-6, assessment is only of Turbuhaler technique (*note that after randomisation, participants <u>should not</u> be using any inhalers other than their study Turbuhalers*).

TURBUHALER ESSENTIAL STEPS

- ☐ 1. Unscrew and remove cover
- ☐ 2. Keep inhaler upright while twisting grip
- ☐ 3. Twist around and then back until click is heard
- ☐ 4. Breathe in strongly and deeply

NOTE: These steps are based on the asthma inhaler technique device specific checklists by the National Asthma Council Australia (http://www.nationalasthma.org.au/health-professionals/primary-care-resources/asthma-inhaler-technique).

Figure 8: Housing Status Questions

PRACTICAL Housing Status Questions

The questions below are to be administered by the Investigator. The Investigator will ask the questions and will record the answers given by the participant. Housing status Questions are to be administered at Visit 1.

1. Did you ever have the house colder than you would have liked during the last winter (June to September)?
   - ☐ Yes, always
   - ☐ Yes, often
   - ☐ Yes, sometimes
   - ☐ No

2. Does your home smell damp or musty?
   - ☐ Yes, always
   - ☐ Yes, often
   - ☐ Yes, sometimes
   - ☐ No

3. Are there damp walls in the living areas of your home, bedrooms, kitchen or lounge?
   - ☐ Yes, always
   - ☐ Yes, often
   - ☐ Yes, sometimes
   - ☐ No

4. Was your house ever so cold that you could see your breath inside during the last winter (June to September)?
   - ☐ Yes, always
   - ☐ Yes, often
   - ☐ Yes, sometimes
   - ☐ No

5. Was your house ever so cold that you shivered inside during the last winter (June to September)?
   - ☐ Yes, always
   - ☐ Yes, often
   - ☐ Yes, sometimes
   - ☐ No

6. How would you describe the condition of your dwelling?
   - ☐ Excellent – No immediate repair and maintenance needed
   - ☐ Good – Minor maintenance needed
   - ☐ Average – Some repair and maintenance needed
   - ☐ Poor – Immediate repairs and maintenance needed
   - ☐ Very poor – Extensive and immediate repair and maintenance needed

7. How many times have you moved house in the last 5 years?
   _____ times

Table: Prednisolone equivalent doses reported by the British National Formulary, accessed April 2014.

Equivalent anti-inflammatory doses of corticosteroids reported by the BNF- **Prednisolone 5mg equals:**
Betamethasone 750 micrograms
Deflazacort 6 mg
Dexamethasone 750 micrograms
Hydrocortisone 20 mg
Methylprednisolone 4 mg
Prednisone 5 mg
Triamcinolone 4 mg

Note the BNF states: This table takes no account of mineralocorticoid effects, nor does it take account of variations in duration of action