Efficacy and safety of a budesonide/formoterol reliever therapy regimen in mild-moderate asthma: A randomised controlled trial

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Abstract

Background

Inhaled corticosteroids taken regularly reduce exacerbation risk in patients with mild asthma. In clinical practice however, adherence to inhaled corticosteroids is poor and the burden of disease from exacerbations is substantive. In this thesis I explore an alternative approach, that of an inhaled corticosteroid/formoterol combination used as sole reliever therapy, that potentially overcomes the problem of poor adherence. I report the results of my research, known as the PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long acting beta agonist (PRACTICAL) study.

Research aims

To investigate the efficacy and safety of as-needed budesonide/formoterol, an inhaled corticosteroid (ICS)/fast-onset long-acting beta agonist (LABA) combination, as compared with maintenance budesonide (ICS) plus as-needed terbutaline, a short-acting beta-agonist (SABA), in adult patients with mild-moderate asthma.

Methods

This research was performed as a 52-week, open-label, parallel-group, multicentre, phase III randomised controlled trial of adults aged 18-75 with mild to moderate asthma using SABA for symptom relief, with or without low to moderate doses of maintenance ICS in the previous 12 weeks. Participants were randomly assigned (1:1) to either: (i) budesonide/formoterol Turbuhaler, an ICS/fast-onset LABA, 200/6 micrograms (μg), one inhalation as needed for relief of symptoms, or (ii) budesonide Turbuhaler, an ICS, 200μg, one inhalation twice daily, plus terbutaline Turbuhaler, a SABA, 250μg, two inhalations as needed. Participants and investigators were not masked to group assignment. Participants were seen for six study visits: randomisation, and at weeks 4, 16, 28, 40 and 52. The primary outcome was rate of severe exacerbations per patient per year, with severe exacerbations defined as the use of systemic glucocorticoids for at least three days because of asthma, or a hospitalisation or emergency department visit because of asthma requiring systemic glucocorticoids.

Findings

Between May 4, 2016 and Dec 22, 2017, 890 participants were assigned to treatment. The analysis included 885 of 890 randomised participants; 437 assigned to budesonide/formoterol as needed and 448 to budesonide maintenance plus terbutaline as needed. 70% of participants were using ICS

at entry. The annualised severe exacerbation rate was lower with as-needed budesonide/formoterol than with maintenance budesonide (absolute rate 0.119 vs 0.172; relative rate, 0.69 [95% confidence interval [CI], 0.48 to 1.00]; p=0.049). The Asthma Control Questionnaire-5 score with budesonide/formoterol was not significantly different from budesonide maintenance (mean difference, 0.06; 95% CI -0.005 to 0.12).

Conclusion

This research has demonstrated that in adults with mild to moderate asthma in the real-world setting, budesonide/formoterol reliever therapy was more effective at preventing severe exacerbations than maintenance low-dose budesonide plus as-needed terbutaline without a clinically important worsening in asthma control.

The evidence presented in this thesis supports the 2019 Global Initiative for Asthma recommendation that inhaled corticosteroid/formoterol reliever therapy is an alternative regimen to maintenance low-dose inhaled corticosteroid and SABA reliever for the prevention of severe exacerbations for patients with mild to moderate asthma.

Publications and Contribution

I finalised the design and set-up of this randomised controlled trial; registering the trial with the Australia and New Zealand Clinical Trials registry, creating patient information sheets, asthma management plans, visit worksheets, study reference manual and data completion manual. I created the crib sheet from which the electronic case report form was created by an external provider. I performed initiation visits at the 15 trial sites including presentations to the site staff on the background and rationale for the study, trial objectives, exclusion and inclusion criteria, procedures, inhaler technique and safety reporting. There followed an open line of communication between me and the clinical trial sites. Supported by a team of people who monitored the study I was able to offer real-time trouble shooting advice. To facilitate participant recruitment in the Wellington region, I approached 45 local GP practices who agreed to support the research, helped the practices to send 17,000 letters to their patients with asthma and fielded phone calls from almost 2000 people keen to learn more about the study. I performed almost 200 of the randomisations and initial visits for the PRACTICAL study alongside follow-up visits. I enjoyed training and managing a team who supported me in the logistics of ensuring that the six visits of the 421 participants who we saw through the Medical Research Institute and Lower Hutt after-hours clinics were timely and appropriately performed. I contributed to the statistical analysis plan and coordinated the four updates that were made to the protocol over the course of the study and their submission for ethical review. I was actively involved in data collection and management. I was supported by Professor Mark Weatherall, statistician, who undertook the statistical analysis and produced a statistical report. I undertook interpretation of the results of the PRACTICAL study and enjoyed presenting the findings at the European Respiratory Society annual congress in 2019.

To date, the following manuscripts have arisen from the research presented in this thesis.

1) Hardy J, Baggott C, Fingleton J *et al*, Budesonide/formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet. 2019 Sep 14;394(10202):919-928.

2) Fingleton J, Hardy J, *et al*, Description of the protocol for the PRACTICAL study: a randomised controlled trial of the efficacy and safety of ICS/LABA reliever therapy in asthma, BMJ Open Respir Res, 2017 Jul 29:4(1)

3) Hardy J, Braithwaite I *et al.* Combined analysis of two randomised controlled trials of budesonide/formoterol reliever therapy in adults with mild or moderate asthma. Submitted for review.

4) Baggott C, Hansen P, Hancox R J, Hardy J *et al.*, What do patients care about most when choosing treatments for mild and moderate asthma? Results from a discrete choice experiment. Submitted for review.

5) Baggott C, Reddel H K, Hardy J *et al,* Patient preferences for symptom driven or regular preventer treatment in mild to moderate asthma – findings from the PRACTICAL study – a randomised clinical trial. Eur Respir J. 2020 Feb 6. pii: 1902073. doi:10.1183/13993003.02073-2019

Information on patient preference for inhaler regimen is not presented in this thesis as this the subject of another candidate's PhD.

The research presented in this thesis has been presented at the following meetings;

1) Oral presentation by J. Hardy at European Respiratory Society Annual Congress J. Hardy, C. Baggott, J. Fingleton *et al.* Open-label trial of budesonide/formoterol reliever therapy in mild asthma. Abstract 21046. Novel findings from asthma clinical trials
2) Poster presentation at European Respiratory Society Annual Conference Christina Baggott, Jo Hardy, Helen Reddel *et al.* What do patients want? Preferences for two asthma regimens in mild/moderate asthma. Poster PA4188.
3) Poster presentation at European Respiratory Society Annual Conference Christina Baggott, Jo Hardy, Helen Reddel *et al.* Discrete choice experiments identifying attributes influencing treatment preference in mild asthma. Poster PA4189.

Additional publications during the period of PhD study using data not derived from this thesis;

1) Fingleton J, Hardy J, Beasley R. Treatable traits of chronic airways disease. Curr Opin Pulm Med. 2018 Jan;24(1):24-31

2) Beasley R, Hardy J, Hancox R. Asthma prescribing: Where are we headed? Respirology. 2017 Nov;22(8):1487-1488

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Thank you to Henry, who took the leap and reluctantly agreed to move to the other side of the world and now doesn't want to leave, and to Ted, the only bona-fide Kiwi in the family.

My greatest thanks are to Professor Richard Beasley, who gave me the opportunity to work on this study, and who has been a constant source of support, friendship and guidance. It has been a huge honour to work for him.

The PRACTICAL Study Group

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Acronyms

Abbreviation	Definition
ACQ	Asthma control questionnaire
AE	Adverse event
ATS	American Thoracic Society
BD	Twice daily (bis in die)
eCRF	Electronic case report form
DSMC	Data safety monitoring committee
ED	Emergency department
ERS	European Respiratory Society
FE_{NO}	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume over one 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
LABA	Long acting beta agonist
NZ	New Zealand
PIS-CF	Participant information sheet-consent form
PRN	As required (pro re nata)
RCT	Randomised controlled trial
SABA	Short acting beta agonist
SAE	Serious adverse event
(S)MART	Single combination ICS/LABA inhaler for maintenance and reliever therapy regimen

1. CHAPTER ONE: INTRODUCTION

1.1 Thesis outline

This thesis will briefly review the definition and pathophysiology of asthma and explore the evolution of the role of inhaled corticosteroids (ICS) and fast-onset long-acting beta agonists (LABA) in its management. A systematic review of the existing literature will explore the evidence behind the use of intermittent ICS. The rationale, methodology and results of the research will be discussed in chapter two of my thesis.

1.2 What is asthma?

There is no gold standard for the definition of asthma. Asthma is defined by the Global Initiative for Asthma (GINA) as a heterogeneous disease, usually characterised by chronic airway inflammation and defined by the history of variable respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough, together with variable expiratory airflow limitation that varies over time and in intensity. Triggers for variations include exercise, allergen exposure, change in weather and viral respiratory infections. [1,2] For reasons of practicality and cost, in primary care the diagnosis of asthma is often made only on the presence of symptoms, which carries the risk of incorrect diagnosis.

Asthma is a huge public health problem, particularly in New Zealand (NZ) where prevalence rates are amongst the highest in the world, with between 15 and 20% of children and adults diagnosed with asthma. [3–5] Asthma affects 334 million people worldwide with a global prevalence of 4.3% (95% CI 4.2 – 4.4). [6,7] It has a huge impact on both a personal and macro-economic level in New Zealand, resulting in 6000 hospital admissions per year, accounting for the greatest cause of years lost to disability for New Zealand males and costing approximately NZ$825 million per year in both direct and indirect costs. [8]

1.3 Pathophysiology of asthma and patterns of inflammation

Asthma is a condition of chronic airway inflammation, features of which continue to be present when symptoms are absent and lung function is normal. [9] Key pathological changes include airway hyper-responsiveness and bronchoconstriction due to hypercontractile airway smooth muscle. Airway wall remodeling resulting in airway thickening and narrowing with resultant airflow limitation is also seen. This is characterised by goblet cell hyperplasia and mucus hyper-production, cilial dysfunction, thickening of the lamina reticularis and reticular basement membrane, growth of

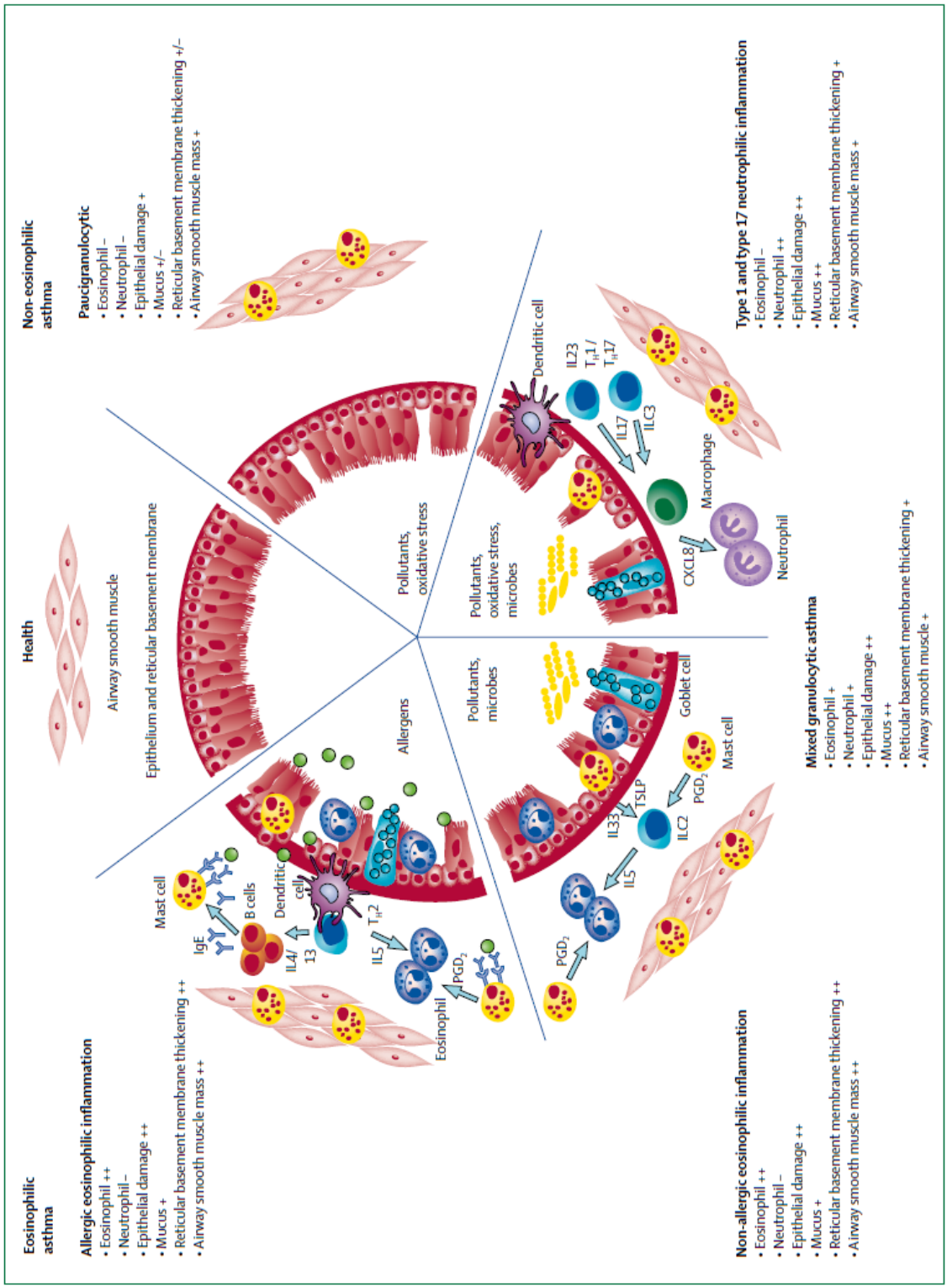
new blood vessels and an increase in airway smooth muscle mass. The amount of airway wall thickening is proportional to the duration and severity of the asthma. [10]

As observed by Papi *et al,* 'the observable characteristics (phenotype) and clinical features of asthma (endotype) are complex and represent a multitude of host-environment interactions that occur over different spatial scales (genes, to cells, to tissue, to organ).' [11]

Individuals can be genetically predisposed to asthma. Single nucleotide polymorphisms at the IL-33, Il1RL1, HLA-DQ and ORMDL-3 loci which code for abnormalities at the epithelial barrier and innate and adaptive immune responses have been implicated in its pathogenesis. [12,13]

The immunology of asthma is heterogeneous with several sub-phenotypes (eosinophilic, neutrophilic, mixed and paucigranulocytic) with differing clinical, inflammatory and functional characteristics. Some asthma phenotypes are identifiable at the time of presentation, for example the atopy, eczema and family history associated with childhood onset allergic-eosinophilic asthma. Non-allergic asthma can be seen at any age, though it is more common in obese women. Late onset asthma is generally non-allergic eosinophilic asthma and more severe, with a faster decline in lung function.[14] Roughly 50% of adult asthmatics have eosinophilic asthma. [15] Eosinophilic asthma has both allergic-dependent and allergic-independent mechanisms. [16] In those with allergic-dependent eosinophilic asthma, an interaction takes place between antigen presenting dendritic cells and T cells. This results in differentiation of the T cells into type 2 helper T cells, indicative of a so-called T2 inflammatory response. These T2 cells secrete cytokines which include IL-4, IL-5 and IL-13 which in turn leads to release of IgE by B cells, as well as mast cell and eosinophilic responses. [17] In non-allergic eosinophilic asthma, innate lymphoid cells, which are defined by the lack of a B or T cell receptor, produce IL-5 and IL-13 when exposed to prostaglandin D2, IL-33 and IL-25. These are released after airway epithelial damage by pollutant particles, bacteria and viruses.

Additional non-T2 type asthma sub-phenotypes are increasingly being identified. Examples include smoking-related neutrophilic asthma, obesity associated asthma and smooth-muscle mediated paucigranulocytic asthma.[18] These sub-types are less well understood. In those with neutrophil predominant disease, cytokines released from T helper 1 cells, T helper 17 cells and type 3 innate lymphoid cells in response to pollutants, oxidative stress and microbes are thought to activate macrophages resulting in release of neutrophil chemokines. [19] The bacterial colonisation often seen in severe asthma may drive a neutrophilic response and, alongside the action of the corticosteroids used in treatment, lead to upregulation of type 1 or type 17 immunity. [20] Each of these inflammatory processes results in the remodeling described in detail above.



• Figure 1: Mechanisms and characteristic pathological features of asthma immunopathology

Papi et al, Lancet 2018 391:783-800. IL= interleukin, T_H= T helper. PDG = prostaglandin D2. TSLP = thymic stromal lymphopoeitin. ILC2 = type 2 innate lymphoid cells. CXCL8 = CXC motif chemokine ligand 8. ILC2 = type 3 innate lymphoid cells. Copyright permission of The Lancet by LANCET PUBLISHING GROUP. Reproduced with permission of LANCET PUBLISHING GROUP in the format Thesis/Dissertation via Copyright Clearance Center.

1.3.1 Fractional exhaled nitric oxide

The subtype distinctions described above are important, as there is growing evidence that patients with T2 inflammation, which can be characterised by raised sputum and blood eosinophils and raised fractional exhaled nitric oxide (FE_{NO}), have a better response to ICS. ICS have been the mainstay of asthma treatment for many years . [18,21–23]

Nitric oxide is generated by the enzyme inducible nitric oxide synthase in the bronchial epithelial cells in response to IL-4 and IL-13. [24] Several studies have demonstrated a correlation between FE_{NO}, bronchoalveolar lavage fluid eosinophils, [25] bronchial biopsy eosinophils, [26] blood eosinophils [27–29] and induced sputum eosinophils. [21,23,30,31] The measurement of FE_{NO} is a simple, quick, safe and non-invasive way of directly measuring T2 airway inflammation.

A number of groups have investigated the normal ranges and cut-off points of FE_{NO}.[32,33] It is widely recommended that a FE_{NO} of 50ppb supports the presence of eosinophilic inflammation, and subsequently an increased likelihood of responding to inhaled corticosteroids. It is suggested that FE_{NO} values between 25 and 50ppb are interpreted cautiously in the clinical context, whilst values of less than 25ppb suggest that eosinophilic airways inflammation is unlikely. The within subject variation for FE_{NO} in healthy subjects is up to 4ppb (around 10%) and this variation increases to 20% in patients with asthma. [34] ATS guidelines suggest the use of FE_{NO} in monitoring airway inflammation in patients with asthma and that a significant response to anti-inflammatory therapy would be a reduction in FE_{NO} of at least 20% for values over 50ppb or more than 10ppb for values lower than 50ppb. [34–36]

There remains significant interest within the respiratory community as to whether FE_{NO} could be used in improving the balance between asthma control and treatment and allow identification of patients for whom an increase in ICS will not improve control.[37] A Cochrane review found no significant reduction in exacerbation risk, symptoms or ICS dose between FE_{NO} guided treatment and guideline based treatment in non-smoking asthmatic adults[38] although FE_{NO} guided treatment does significantly reduce exacerbation rate compared to guideline based treatment in children.[39] It seems that further studies are needed to further characterise the population most likely to benefit from FE_{NO} guided treatment and determine the frequency that FE_{NO} needs to be monitored in this context. As such, the routine titration of asthma medication based on FE_{NO} is not currently advised.

Importantly, FE_{NO} is not thought to be useful as a predictor of asthma control. [40–43] Patients are not always symptomatic or suffering from exacerbations in the presence of airway inflammation.[44]

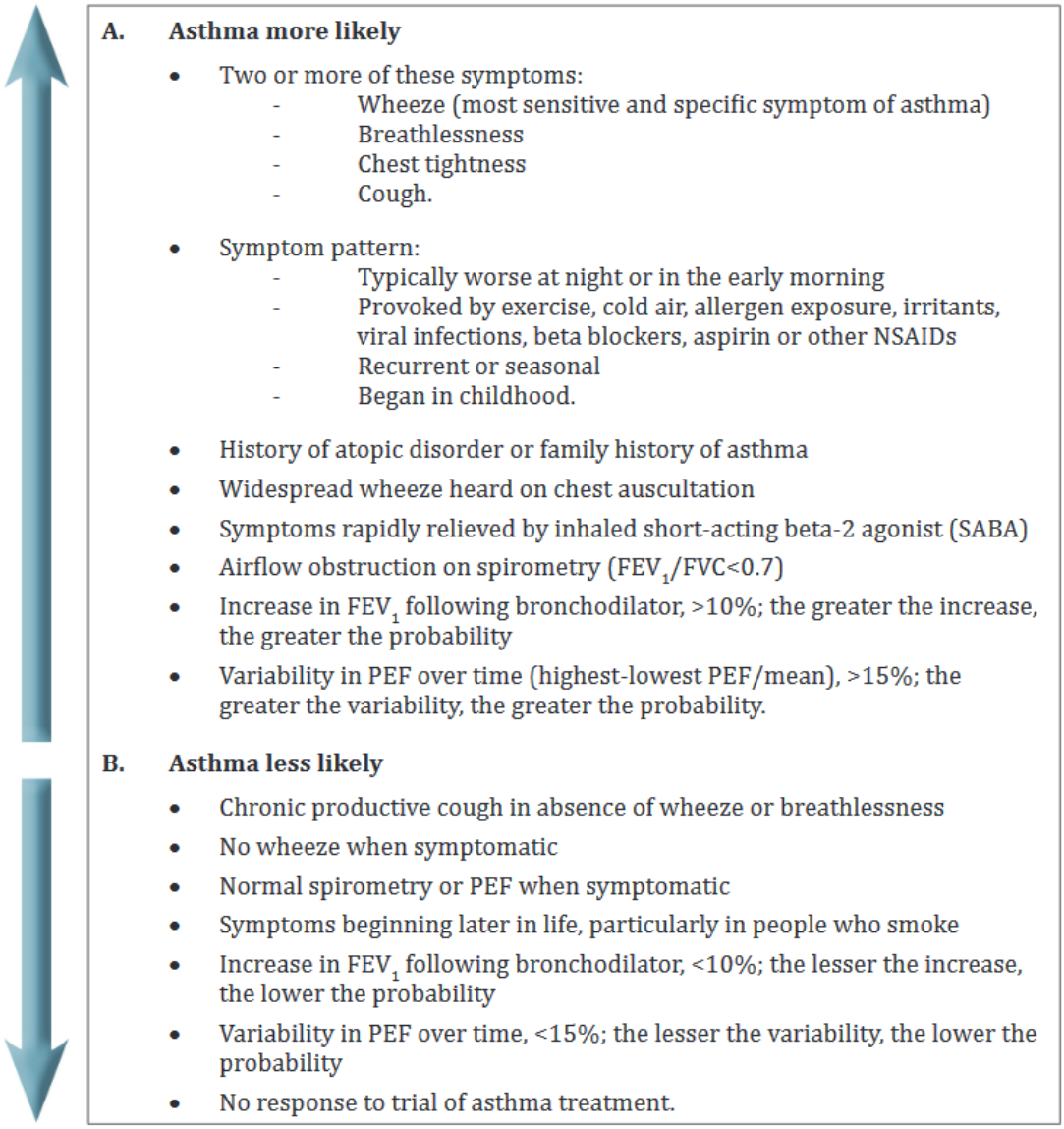
Some individuals may have a raised FE_{NO} despite having well-controlled asthma, and this is thought to be due to more than one factor, i.e., not only eosinophilic airway inflammation causing the raised FE_{NO}.

It is postulated that a raised FE_{NO} can predict a faster rate of decline in lung function and several studies have found a link between forced expiratory volume in one second (FEV1) decline and airway inflammation. [45–47] A recent study demonstrated an accelerated decline in FEV1 in all patients with a FE_{NO} value of more than 57ppb. [48] As highlighted in a recent editorial, it remains unclear if airway inflammation as measured by FE_{NO} is sufficient to lead to more rapid decline in lung function, or whether exacerbations are required in addition to this. [49]

There remains insufficient data on the role of FE_{NO} in monitoring response to therapy and there is a recognised need for FE_{NO} to be included as an end point in future clinical trials.

1.4 Asthma symptoms, clinical presentation and investigation

Asthma symptoms, which include cough, wheeze and shortness of breath are non-specific, and assessing the likelihood of an asthma diagnosis relies on a careful history of triggers and timing of symptoms.



• Figure 2: Factors which affect the likelihood of an asthma diagnosis

Reproduced with permission from the New Zealand Adult Asthma Guidelines 2016, Asthma and Respiratory Foundation New Zealand.

The diagnosis of asthma is probability based and takes account of symptoms and the presence of variable expiratory airflow obstruction. [11] Variable airflow obstruction can be demonstrated in several ways including bronchodilator reversibility testing. A positive test would find an increase in FEV_1 of more than 12% and more than 200mL, 15 minutes after administration of a rapid onset

beta agonist. Of note, a negative test does not exclude a diagnosis of asthma. Bronchial challenge tests using mannitol are also used and a positive test and the presence of airway hyper-responsiveness is supported by a fall in FEV_1 of more than 20% alongside a fall in the FEV1 to forced vital capacity (FVC) ratio. A peak flow diary, demonstrating within day variability of more than 10% can also be used. The greater the variability in airflow and the more often variability is seen, the more likely asthma is as a diagnosis.

1.5 What is asthma control?

The two constituents of asthma control can be summarised as comprising 'symptom burden' (day to day symptoms, disturbed sleep and activity limitation) and the risk of adverse outcomes (exacerbations, persistent airflow limitation, medication side-effects)' [11]. As such, no single primary end point is completely suited as a single measure of asthma control. Patients who achieve well-controlled asthma based on a combined measure of symptom burden and adverse outcomes have greater improvements in quality of life than if improvement in only one aspect is considered, so that a composite of end points gives a more representative picture of asthma control. [50]

Uncontrolled asthma symptoms are associated with an increased risk of suffering an asthma exacerbation. That said, exacerbations can be preceded by a period of well-controlled asthma, and patients with mild disease do experience serious outcomes. [51,52] Assessment of symptom burden alone is not therefore an adequate assessment of asthma control.

That said, an assessment of asthma symptom frequency does contribute to the assessment of asthma control, and there are several questionnaires to aid this assessment. The asthma control questionnaire (ACQ-5) has been validated to assess, from the patient's perspective, the presence of asthma symptoms including breathlessness, nocturnal waking, symptoms on waking, activity limitation and wheeze in the previous week. [53–56] The asthma related quality of life questionnaire (AQLQ) is a global measure of the impact of asthma on a patient's day to day quality of life. Both questionnaires depend on good patient recall, on the patient being aware of their symptoms and on the patient's own perception of what asthma control is, which can differ widely from a physician's definition. [57]

The New Zealand adult asthma guidelines [58] endorse the GINA strategy in suggesting cut offs for good, partial and poor asthma control based on frequency of daytime symptoms, frequency of reliever use per week, activity limitation and presence of asthma symptoms during the night and on waking. This is considered alongside assessment of the risk of adverse outcomes including

exacerbations, mortality and treatment related adverse effects. This assessment of asthma control is regardless of current treatment.

Good control	Partial control	Poor control
All of: • Daytime symptoms ≤2 days per week • Need for reliever ≤2 days per week† • No limitation of activities • No symptoms during night or on waking	One or two of: • Daytime symptoms >2 days per week • Need for reliever >2 days per week† • Any limitation of activities • Any symptoms during night or on waking	Three or more of: • Daytime symptoms >2 days per week • Need for reliever >2 days per week† • Any limitation of activities • Any symptoms during night or on waking

† Not including SABA taken prophylactically before exercise. (Record this separately and take into account when assessing management.)
Note: Recent asthma symptom control is based on symptoms over the previous four weeks.
Source: Adapted from Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. GINA; 2012. Australian Asthma Handbook v1.1 asset ID:33.

- Figure 3: New Zealand Asthma guideline definitions of asthma control

Reproduced with permission from the New Zealand Adult Asthma Guidelines 2016, Asthma and Respiratory Foundation New Zealand.

As tabulated below, several other factors including beta agonist overuse, not receiving an inhaled corticosteroid, as well as psychological and socioeconomic problems, are important contributors to a patient's risk of an asthma exacerbation and therefore poor asthma control.

A.	**Asthma**
•	Poor symptom control
•	Hospitalisation or ED visit in the last year
•	High SABA use (>1 canister per month)
•	Home nebuliser
•	History of sudden asthma attacks
•	Impaired lung function (FEV_1 < 60% predicted)
•	Raised blood eosinophil count
•	ICU admission or intubation (ever)
•	Requirement for long-term or repeated courses of oral corticosteroids.
B.	**Comorbidity**
•	Psychotropic medications
•	Major psychosocial problems
•	Smoking
•	Alcohol and drug abuse
•	Aspirin or other NSAID sensitivity.
C.	**Other factors**
•	Underuse or poor adherence to ICS treatment
•	Discontinuity of medical care
•	Socioeconomic disadvantage
•	Māori and Pacific ethnicity
•	Occupational asthma.

- Figure 4: Clinical features associated with increased risk of severe exacerbations and mortality

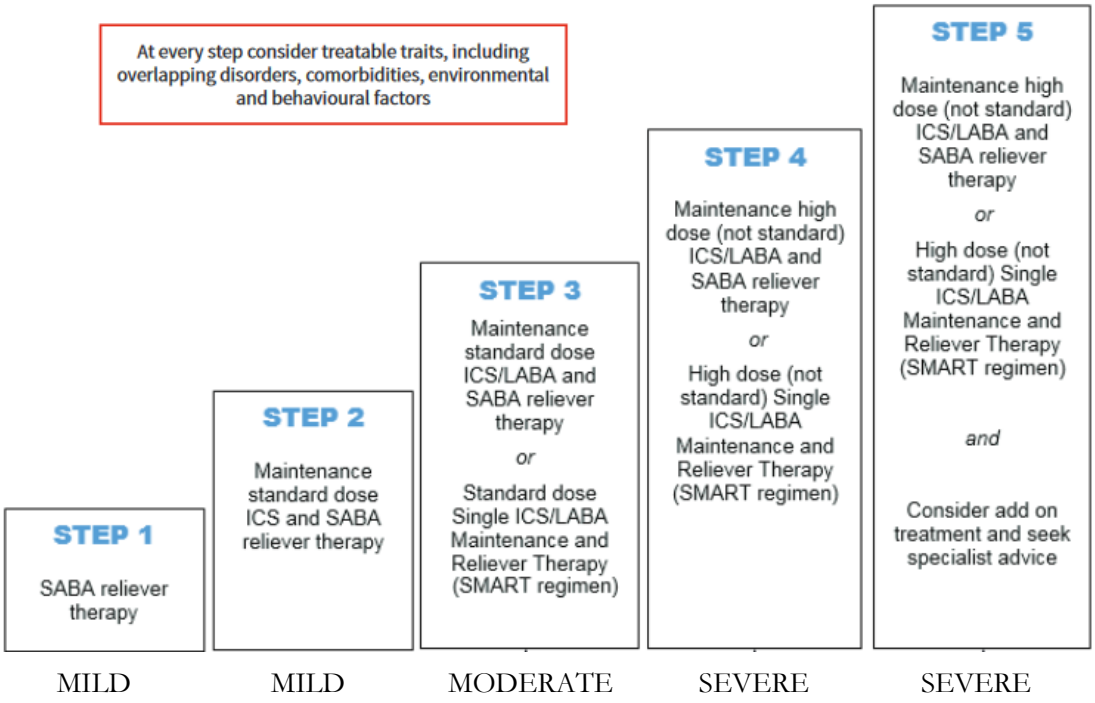
Reproduced with permission from the New Zealand Adult Asthma Guidelines 2016, Asthma and Respiratory Foundation New Zealand.

1.6 Severity of asthma

There are no objective markers of disease severity in asthma. Indeed, as demonstrated in the U-BIOPRED study [59] inflammation cannot be used as a marker of severity as 'severe asthma exists despite suppressed tissue inflammation within the proximal airway wall' and inflammation is found even in those with mild intermittent asthma. To this end, the GINA 2019 report states that asthma severity is best described retrospectively as 'the level of treatment required to control symptoms and exacerbations once the patient has been on controller treatment for several months' and modifiable factors such as poor adherence, smoking and comorbidities have been excluded. [1]

The pharmacological management options for the treatment of asthma fall into three categories; relievers, preventers and add-on biological therapies. Reliever therapies are provided to all patients with asthma and include SABA such as salbutamol and terbutaline. As described above, one measure of asthma control is the frequency with which a reliever medication is used for the relief of breakthrough symptoms. Controller medications are used to improve symptom control and reduce the risk of exacerbations. Controller medications include those containing ICS such as budesonide or fluticasone, with or without a LABA such as formoterol. Add-on therapies including tiotropium, leukotriene receptor antagonists, macrolide antibiotics and biological therapies can be considered in patients with persistent symptoms despite high dose controller medications.

As Figure 5 below illustrates, mild asthma is that which is well-controlled with Step 1 or Step 2 treatment, e.g. regular low dose ICS. Moderate asthma is that which is controlled with Step 3 treatment, e.g. regular low dose ICS and long acting beta agonist (ICS/LABA) combination inhaler or moderate dose ICS (eg, 800μg budesonide/day). Severe asthma is that which requires Step 4 or 5 treatment, e.g. regular high dose ICS/LABA to prevent it from becoming uncontrolled or asthma that remains uncontrolled despite treatment. [1,57,60] Figures 6 and 7 demonstrate standard daily doses of ICS and ICS/LABA.



• Figure 5: Classification of asthma severity and recommended pharmacological management

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Beclomethasone dipropionate	400–500 µg/day
Beclomethasone dipropionate extrafine	200 µg/day
Budesonide	400 µg/day
Fluticasone propionate	200–250 µg/day

• Figure 6: Recommended standard daily dose of inhaled corticosteroid in adult asthma

Reproduced with permission from New Zealand Adult Asthma guidelines 2016, Asthma and Respiratory Foundation New Zealand.

Recommended ICS/LABA doses in adult asthma			
Step 3		**Step 4 + 5**	
FP/Salm 50/25 2 inh BD	+ SABA for relief	FP/Salm 125/25 2 inh BD	+ SABA for relief
FP/Salm 100/50 1 inh BD	+ SABA for relief	FP/Salm 250/50 1 inh BD	+ SABA for relief
Bud/Form 100/6 2 inh BD	+ SABA for relief	Bud/Form 200/6 2 inh BD	+ SABA for relief
Bud/Form 200/6 1 inh BD	+ SABA for relief	FF/Vilanterol 100/25 1 inh OD	+ SABA for relief
		[FF/Vilanterol 200/25 currently not funded]	
Or		Or	
SMART regimen		SMART regimen	
Bud/Form 100/6 2 inh BD	+ 1 inh for relief	Bud/Form 200/6 2 inh BD	+ 1 inh for relief
Bud/Form 200/6 1 inh BD	+ 1 inh for relief	[Bud/Form 400/12 is not recommended]	

FP/Salm: Fluticasone Propionate/Salmeterol; Bud/Form: Budesonide/Formoterol; FF/Vilanterol: Fluticasone Furoate/Vilanterol; OD: once daily; BD: twice daily; SMART: Single ICS/LABA Maintenance and Reliever Therapy.

- Figure 7: Recommended standard daily doses of ICS/LABA at Step 3,4 & 5

Reproduced with permission from New Zealand Adult Asthma guidelines 2016, Asthma and Respiratory Foundation New Zealand.

1.7 What is an exacerbation of asthma?

On a background of chronic inflammation, asthmatics have episodic deteriorations, outside the range of their usual day to day symptoms, known as exacerbations. One of the main focuses of asthma management is to prevent these, given the associated anxiety and short and long term risk to patients and cost to the healthcare system. [61] The ATS/ERS consensus document [2] describes a severe asthma exacerbation as 'use of systemic corticosteroids or an increase from a stable maintenance dose, for at least three days and/or a hospitalisation or emergency department visit because of asthma requiring a course of systemic corticosteroids'. There are no validated criteria for a severe exacerbation that include change in peak flow or beta agonist reliever use and characterisation of the 'clinical, psychological and contextual factors that contribute to patient decisions to seek healthcare professional review and physicians to prescribe corticosteroids' require further characterisation and are not standardised. [2]

A moderate exacerbation is defined in the same document as 'an asthma event that lasts for more than two days, that is troubling to the patient, with a deterioration in symptoms and/or lung function and that needs a prompt, temporary change in treatment, but that is not severe and does not warrant systemic steroid use or require hospitalisation.' [2]

The same consensus group felt that it was not possible to define mild asthma exacerbations as they were just outside the range of normal asthma variation and therefore not possible to differentiate from a 'transient loss of asthma control'.

Exacerbations can happen to all asthmatics whatever the severity of their asthma, though exacerbations are more common in patients with more severe asthma.[62] Of note, mild asthmatics can have severe asthma exacerbations. 30–37% of adults presenting to emergency departments with acute asthma, [51] 16% of patients with near-fatal asthma, [52] and 15–20% of adults dying of asthma [52,63] experienced symptoms less than weekly in the previous three months. Allergens, irritants, bacterial and viral infections can trigger an exacerbation and the immunopathology is thought to vary depending on the trigger. For example, virus induced exacerbations are associated with a neutrophilic airway infiltration, whilst allergen induced exacerbations are associated with eosinophilic infiltration. 57% of adult asthma exacerbations are thought to be due to upper respiratory tract infections. [64] Rhinovirus, the cause of the common cold, is the virus most commonly associated with exacerbations and is known to induce a decrease in beta adrenoceptor function, the receptor on which reliever medications such as salbutamol work. [65]

1.7.1 Why are exacerbations harmful?

Severe exacerbations of asthma, associated with an increase in airway inflammation, are associated with an accelerated deterioration in lung function.[66] In a study of 128 non-smoking patients followed up over a three-year period, patients with no severe exacerbations had an average 13.6mL/year fall in FEV1, those with one exacerbation an average 41.3mL/year fall in FEV1 and those with two or more exacerbations an average 58.3mL/year fall in FEV1; $p < 0.01$ and $p < 0.0001$, respectively. [67]

A severe exacerbation reflects pathological changes in the airways, which result in long term structural and functional changes. Consideration of both those short term implication of severe exacerbations such as cost to the healthcare system, days off work and distressing symptoms and long term implications such as structural and functional airway changes supports the use of severe exacerbation rate as an end point in clinical trials. [2]

1.8 Ongoing morbidity

Despite our increasing understanding of the pathophysiology of asthma, clear diagnostic guidelines and management strategies on the step-wise up-titration of asthma treatment, significant morbidity persists in the 'silent majority' that make up the mild and moderate asthma population. Patients with apparently mild asthma are still at risk from near-fatal and fatal asthma attacks. The UK National Review of Asthma Deaths (NRAD) found that 9% of asthma deaths were in patients prescribed SABA treatment alone, suggesting that their doctor thought that they had mild asthma. [68] In the OPTIMA study, 33% of patients with mild asthma who were using a SABA only at baseline and throughout the study suffered a severe asthma exacerbation requiring a course of oral steroids. [69] Two additional randomised controlled trials of well-controlled ICS-treated patients who did not have an exacerbation in the run-in period found that the annual rate of severe exacerbations requiring medical intervention was 35%. [70,71]

Why does this morbidity persist? Numerous studies have shown low adherence to guidelines and failure to prescribe ICS on the part of prescribers. [72–75] Until recently guidelines would suggest that if a patient is taking their SABA reliever anything more than twice per week, then a regular ICS preventer inhaler should be considered. Several surveys show that neither doctors nor patients consider this as representing uncontrolled asthma requiring an up-titration in treatment. [72–75] Additionally, patients adhere poorly with their prescribed ICS increasing their SABA reliever use when symptoms worsen, but not necessarily their maintenance preventer use as they notice no immediate improvement in symptoms with it. [76–78] Prescription refill rates suggest that patients use an average of between two and four canisters of ICS per year.[79,80] In a study performed at the Medical Research Institute of New Zealand (MRINZ) using electronic monitors, only 39% of patients took at least 80% of their prescribed ICS dose. [81] In a study of patients admitted to hospital with severe exacerbations of their asthma, within one week of discharge adherence to inhaled steroid had dropped to 50%. [82] An estimated 24% of severe exacerbations are attributable to medication non-adherence. [83]

It has been argued that medical professionals contribute to this learned behaviour of poor adherence and that in prescribing a SABA, with no anti-inflammatory properties at the point of diagnosis, we are teaching patients that treating symptoms alone is admissible. We then proceed, at GINA step 2, to remove the emphasis on symptom recognition as a trigger to asthma medication use and switch to asking patients to take a medication regularly regardless of symptoms. This requires a behaviour to be un-learnt and the need to remember which inhaler to use and when. To

add to this, the regular maintenance treatment added at step 2 does not result in any rapid change in symptoms, reinforcing the perception that the ICS is inferior to the SABA. [84]

An additional factor contributing to medication non-adherence and the morbidity seen in asthma is the disconnect seen in patients between actual asthma control and symptoms and exacerbations. Patients can regard their asthma as controlled and not serious despite experiencing symptoms and exacerbations. Many patients perceive their asthma as well-controlled if they are able to manage their exacerbations with medical help or medication rather than as a lack of day to day asthma symptoms.[85] This was demonstrated in a Europe-wide online survey of 8000 asthmatics in which 45% of respondents had uncontrolled asthma. In this survey, of the 44% who had required a course of steroid tablets in the past year, 75% regarded their asthma as not serious. [86] The AIRE study confirmed these findings, with 50% of patients who had severe persistent symptoms reporting that their asthma was well-controlled. [73]

Several groups have suggested strategies to improve adherence. These have included patient education, use of asthma self-management plans, audio-visual reminders, closer follow-up, medication reminders and simplification of treatment regimens by reducing the number of inhalers. [81,87–89] Use of an ICS/LABA combination inhaler increases ICS refill rates compared with ICS alone in a single inhaler or ICS and LABA in two separate inhalers, and prevents the risks associated with LABA monotherapy. This makes symptom driven use of an ICS/fast-onset LABA inhaler an attractive option in improving ICS adherence. [79,90,91]

1.9 Pharmacological treatment

1.9.1 Short-acting beta agonists

In order to address the ongoing morbidity and mortality described above, there is a clear need for a new management strategy that accounts for both the risk of severe asthma exacerbations despite minimal day to day symptoms, and the difficulty committing to a regular ICS when symptoms are intermittent. I will proceed to discuss conventional treatment strategies to date to inform what these novel approaches might be.

The adrenergic agonists used to manage the symptoms of people with asthma have evolved over the past 100 years from epinephrine to isoproterenol, a non-selective beta agonist, in the 1940s and onwards in the 1960s to the development of the more selective beta agonist salbutamol. In the 1980s, the long acting beta agonists salmeterol and formoterol, with a half-life of more than 12 hours, became available.

When diagnosing a patient with asthma, current widespread practice would be the prescription of a SABA, such as salbutamol or terbutaline to use intermittently for the relief of symptoms. In countries such as Australia, SABA are available over the counter from pharmacies and are often used without regular medical supervision. This can result in under treatment as although SABA relieve symptoms rapidly, they do not have any anti-inflammatory action and therefore have no effect on preventing exacerbations or airway remodelling, masking the underlying problem. [92,93]

Salbutamol and terbutaline are the most commonly prescribed SABAs [94] and are selective, beta 2 adrenoceptor agonists with a dose response bronchodilatory effect. [95] They can be used as relievers as maximal bronchodilation occurs within 30 minutes and lasts for up to six hours. Side effects include tachycardia, palpitations, tremor, hypokalaemia and muscle cramp. [95,96]

Until recently, guidelines recommended that all patients with asthma should be prescribed a SABA and supported its symptom guided use. Patients report high satisfaction and reliance on inhaled SABA due to its rapid relief of symptoms, low cost and use in the secondary care management of exacerbations. [97,98] A paradox is that within one to two weeks, regular use increases bronchial hyper-responsiveness with an associated increase in treatment requirements, symptom burden and diurnal variation in lung function. [99–101] More frequent SABA use has been associated with future exacerbation risk, [97] hospital admission,[102] increased levels of airway inflammation [103] and mortality. [98,104] Co-administration with an ICS counteracts these deleterious effects but as already discussed some patients only have access to SABA monotherapy or are non-adherent with their ICS

maintenance treatment. [105–107] Counter-intuitively, initial unopposed prescription of SABA also delays prescription of ICS. [86,108,109]

It would seem surprising that SABA monotherapy, which has no inherent anti-inflammatory properties, has been suggested in guidelines at all, particularly given evidence that maintenance ICS with a SABA reliever results in around a 50% reduction in severe exacerbations, better symptom control and improved quality of life. [69,110] Use of SABA monotherapy is an historic approach, targeting symptoms rather than any underlying mechanism and dates from a time when asthma was thought of as a condition only of bronchoconstriction. As discussed above, it is now well established that asthma is a condition in which episodes of worsening inflammation result in an increase in symptoms and exacerbations. [84]

Opponents would argue that patients with sporadic symptoms are unlikely to take regular daily ICS due to a lack of perceived necessity, side effects and cost. [111,112] As will be discussed subsequently, this highlights the question of whether an ICS/fast-onset beta agonist combination inhaler used to relieve symptoms and titrated to symptom frequency and severity would be an approach that would better reflect patient behaviour and preference. This approach would overcome low rates of ICS adherence, prevent unopposed excessive SABA use and prevent any contradictions in messaging between Step 1 and Step 2. [113]

1.9.2 Beta agonists - concerns

There has been intense speculation as to the efficacy and safety of beta agonists over the past 50 years.[114] Firstly, there was an epidemic of asthma deaths in the United Kingdom in the 1960s related to a rise in prescription of isoproterenol forte.[115] Second was an epidemic of asthma deaths in New Zealand in the 1970s and 1980s explored in a series of case control studies. These studies reported that Fenoterol increased the risk of asthma mortality. [116–121] The fenoterol product available on the market was four times the strength of salbutamol given the dose in each puff and its potency and following its withdrawal from the market the mortality rate fell. Fenoterol is also a full $beta_1$ agonist and associated with significant cardiac side effects. The third was the Saskatchewan Asthma Epidemiology Study in which investigators used a linked health insurance database of 12,301 patients to perform a matched case control study and found that the use of fenoterol was associated with an increased risk of death from asthma (odds ratio 5.4 per canister with fenoterol as compared to 2.4 with albuterol).[98,122] Finally, two studies demonstrated that the LABA salmeterol, when used without an ICS, was associated with an increased risk of asthma related adverse events. [123,124] The first of these was an impressive GP-based study in which 25,180 patients with asthma who needed

a bronchodilator reliever were randomised to use either salmeterol (LABA) or salbutamol (SABA) for 16 weeks alongside their pre-existing baseline treatment. There were fewer withdrawals in the salmeterol group compared to salbutamol (2.91 versus 3.79% p=0.0002) with a non-significant increase in asthma related deaths in the salmeterol group (0.07 versus 0.02% p=0.105). There was no measure of adherence to the study medication, and 31% of subjects were not taking ICS at the point of study entry such that patients would have received LABA monotherapy. [124]

Finally, the Salmeterol Multicenter Asthma Research Trial (SMART) was a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol.[124] The study was a 28-week randomised, placebo controlled trial of 26,355 adult participants not already taking a LABA which ran between 1996 and 2003. Participants were randomised to receive 42μg of salmeterol twice daily or placebo twice daily whilst their usual asthma treatment was continued. Follow-up was by monthly telephone consultation. The target sample size was 60,000 and the study was stopped when an interim analysis showed a small but significant increase in asthma related death for patients, particularly those of African American heritage, taking salmeterol as compared with those taking placebo. There were seven deaths in patients taking ICS at baseline (four on salmeterol and three on placebo) and nine deaths in patients not taking ICS (all nine patients were randomised to receive salmeterol). The risk of death associated with salmeterol was about one in 700 patient-years of treatment. The study precipitated a black box warning issued by the US Food and Drug authority on both salmeterol and salmeterol-fluticasone (Seretide®). [125,126] At face value, the suggestion might be that the SMART study showed that use of a LABA was associated with an increase in asthma related death. On closer review, the SMART study provides evidence that LABA should not be prescribed alone as the rate of asthma related death and life-threatening events is equal in both salmeterol and placebo groups in those taking ICS at baseline.

LABAs alone do not have any anti-inflammatory effects though they do have some immunomodulatory properties. As such, LABAs can improve asthma symptoms whilst masking but not treating underlying airways inflammation. This was demonstrated in the SOCS study in which 164 patients with asthma which was well-controlled on ICS (triamcinolone 400μg twice daily) were randomised to either continue taking triamcinolone, switch to a LABA (salmeterol 52μg twice daily), or to a placebo for four months. In this randomised, double-blinded study, symptoms remained well-controlled on LABA but there was evidence of greater airway inflammation with a higher rate of asthma exacerbations (20% LABA group versus 7% ICS group, p=0.04) and greater increases in sputum eosinophils seen in the LABA group (2.4% [0.0% to 10.6%] vs −0.1% [−0.7% to 0.3%]; p<0.001). [127]

A subsequent meta-analysis compared LABA (salmeterol) with non-LABA treatments and stratified by ICS use. In studies in which patients were randomised to receive an ICS/LABA combination, there was no increase in death, hospital admission or intubation for asthma. The odds ratio for risk of asthma related death was 7.3 (95% CI 1.8, 29.4) in patients not prescribed ICS. [128] An additional meta-analysis of 42 trials including 13,542 LABA (formoterol) randomised patients and 9968 non-LABA patients of whom approximately 90% were receiving an ICS confirmed these findings, with no increased risk of asthma-related death in those taking ICS/LABA. [129]

In summary, it can be concluded that LABAs should not be prescribed other than in a combination inhaler to patients with asthma. LABAs, when used alone, provide symptomatic relief without addressing increasing airway inflammation, resulting in delays in seeking medical attention and therefore an increase in asthma related morbidity and mortality. [130–137]

1.9.3 Fast-onset long-acting beta agonists

With its fast onset of action, the LABA formoterol is an efficacious bronchodilator when used as a reliever with comparable efficacy to the SABA salbutamol. In crossover studies as needed reliever formoterol improved lung function and subjective asthma control, and was perceived by patients as being more effective as compared to as-needed salbutamol. [138–144] Formoterol demonstrates 80-90% of its maximal bronchodilating effect within five to ten minutes of inhalation. In contrast, the long acting beta agonist salmeterol takes 60 minutes to reach its maximal bronchodilating effect. Formoterol is the only LABA whose onset of action is rapid enough for it to be used as a reliever. [142,145] This fast onset is a result of its water solubility and moderate lipophilicity which facilitates rapid diffusion to the beta receptor on the airway smooth muscle. Formoterol has a long duration of action as its lipophilic properties allow it to remain in the airway tissue. Its effects are maintained for 12 hours. The systemic side effects last only as long as those of a SABA. [143]

Formoterol is a full agonist with high intrinsic activity. It is rapid and long lasting and can therefore be used in the management of acute asthma attacks [146–148] as well as in maintenance treatment. Combined with an ICS to protect against unopposed LABA use, formoterol therefore has the potential to replace the SABAs described above, reducing the number of different inhalers a patient is necessitated to use. [139,144]

1.9.4 Inhaled corticosteroids

Inhaled corticosteroids have remained the mainstay of asthma treatment since the 1970s.[149] They exert their effect by binding glucocorticoid receptors located in the cytoplasm of airway epithelial cells, forming a dimer that binds to DNA and regulates gene transcription. This in turn reduces the number of inflammatory cells, including dendritic cells and eosinophils, in the airways resulting in reduced airway hyper-responsiveness within hours of administration. [150–154]

Recommendations for the early prescription of ICS are based on several Cochrane systematic reviews that have demonstrated that regular use of ICS reduces hospital admission and readmission, reduces asthma mortality rates, reduces symptoms and improves lung function. [106,155–158]

1.9.4.1 When should an ICS be initiated?

For the past 25 years, guidelines have consistently recommended a symptom based cut-off of asthma symptoms more than twice per week for the initiation of an inhaled corticosteroid. To assess whether this symptom based cut-off for initiation of ICS was appropriate, Reddel *et al* performed a post-hoc analysis of the START study having found minimal evidence for this recommendation in their preparation of the GINA report in 2014. [109,159,160] The START study was a pharmaceutical-company funded, three-year, multinational, randomised, double-blinded placebo-controlled study designed to determine if the treatment of mild asthmatics with low-dose, once daily ICS prevents serious asthma related events such as hospitalisation and reduction in lung function. In the post hoc analysis of the study, patients were stratified based on baseline symptom frequency. Use of a once daily ICS was found to increase time to first severe asthma related event, halve the risk of a severe exacerbation of asthma and reduce the rate of decline in lung function irrespective of asthma symptom frequency. This led the authors to suggest that perhaps regular ICS should be prescribed 'on the basis of population risk rather than on an individual's symptom frequency'. This is unlikely to be popular with either asthmatic patients or prescribing physicians due to the previous mentioned perceptions around what constitutes uncontrolled asthma and poor adherence.

1.9.4.2 Evidence of dose response and side effects

There is evidence that asthma control in mild to moderate asthmatics is ICS dose dependent, but that the most benefit is gained at low to moderate ICS doses with a steep increase in side effects and little improvement in asthma control for patients taking higher doses. [150,161–165]

The most common side effects from inhaled corticosteroids are local. Hoarse voice, oral candidiasis, sore throat and cough are the most prevalent. Oral candidiasis affects around 5% of adults taking ICS and is best prevented by mouth rinsing and gargling after ICS use. [166] Hoarse voice occurs in up to 58% of patients taking ICS via a metered dose inhaler (MDI) though this is lower when the ICS is delivered via a Turbuhaler. [150] Extensive studies on patients with variable asthma severity have found minimal systemic effects in terms of bone health, growth, skin health and metabolism at doses of up to 800μg per day of ICS.[167]

1.9.4.3 ICS dosing frequency during an exacerbation

A Cochrane review of eight randomised controlled trials, including five adult studies (n=1247) in which the ICS dose was variably doubled, increased four-fold or five-fold, concluded that available evidence did not support increasing ICS dose to treat exacerbations. [168] Prior to this, based on consensus, most asthma guidelines had recommended a doubling of the dose of maintenance ICS early in an asthma exacerbation. Individually, two of these trials demonstrated that doubling the dose of ICS as asthma worsened did not prevent the need to take oral corticosteroids to treat an exacerbation. [169,170] Quadrupling the dose has been found to be beneficial however, with a number needed to treat of 15 (95% CI nine to 43) in a recent study. [171] As expected, the intervention group saw an associated higher frequency of treatment related adverse effects such as oral candidiasis. [171–173]

The default in current clinical practice is the prescription of oral corticosteroids such as prednisone when patients present with an asthma exacerbation. Based on these data, in patients experiencing an asthma exacerbation it could be argued that the maintenance dose of ICS be quadrupled once symptoms increase and peak flow falls and only if the deterioration is more severe should a short course of oral prednisone be started. That said, increasing the frequency of the ICS dose to a four times a day regimen whilst maintaining the same total daily dose improved control in unstable asthma in a small study. [174] It seems likely that the timing of ICS administration is more important in determining efficacy that the total ICS dose.

1.9.5 Combining LABA and ICS

1.9.5.1 Asthma control

Given the limited dose-response characteristics of ICS discussed above, adding an additional medication to obtain asthma control is appealing. The seminal clinical observation on the additive effect of adding LABA to ICS was that made by Greening *et al* in 1994. In this study, 426 asthmatics

whose asthma was not well-controlled on ICS (beclomethasone 200μg twice daily), were randomised to receive either a LABA (salmeterol xinaforte 50μg twice daily) and an ICS (beclomethasone 200μg twice daily) in separate inhalers, or single higher dose ICS (beclomethasone 500μg twice daily). An improvement in morning peak flow was seen in both groups but this was greater in the ICS/LABA group as were asthma symptoms and rescue inhaler use. Exacerbation rates were equal in each group. Thus adding in a LABA was more effective than more than doubling the dose of inhaled steroid, [175] a finding confirmed in a double blind study of 738 subjects across 72 centres. [176]

A number of subsequent studies and meta-analyses have confirmed these findings including the Gaining Optimal Asthma Control study (GOAL) of 3421 subjects. In this study subjects with uncontrolled asthma were randomised to receive either ICS (fluticasone) or ICS/LABA (fluticasone/salmeterol). The ICS dose was up titrated at three monthly intervals until total control was achieved or a maximum ICS dose of 500μg twice daily was reached. 28% of ICS only versus 41% of ICS/LABA subjects achieved total asthma control. 59% of ICS only versus 71% of ICS/LABA subjects achieved well-controlled asthma confirming the superior efficacy of the ICS/LABA combination in achieving asthma control. [62]

1.9.5.2 Exacerbations

The FACET study was the first to suggest that the addition of LABA to ICS could reduce the frequency of severe asthma exacerbations. [177–179] In the study, 852 patients were randomly assigned to one of four treatment arms; ICS (budesonide 100μg) plus placebo, ICS (budesonide 100μg) plus fast-onset LABA (formoterol 12μg), high dose ICS (budesonide 400μg) plus placebo, or high dose ICS (budesonide 400μg) plus fast-onset LABA (formoterol 12μg). Adding formoterol to the lower doses of budesonide resulted in a 26% fall in the rate of severe exacerbations and a 40% fall in the rate of mild exacerbations. The study found that the most effective strategy for reducing severe exacerbations, which were defined as requiring a course of oral corticosteroids, was a quadrupling of the dose of budesonide from 200 to 800μg per day. Adding in formoterol further reduced the rate of severe exacerbations.

The MIASMA study, Masoli *et al* meta-analyses and the OPTIMA study further built on this, finding that in patients already receiving ICS, adding formoterol was more effective than doubling the corticosteroid dose in reducing severe exacerbations and improving asthma control. [69,180,181] The RELIEF study compared as-needed formoterol 6μg with salbutamol 200μg over a six-month study period. 76% of patients were on ICS and 31% also on LABAs at the point of study entry. The time

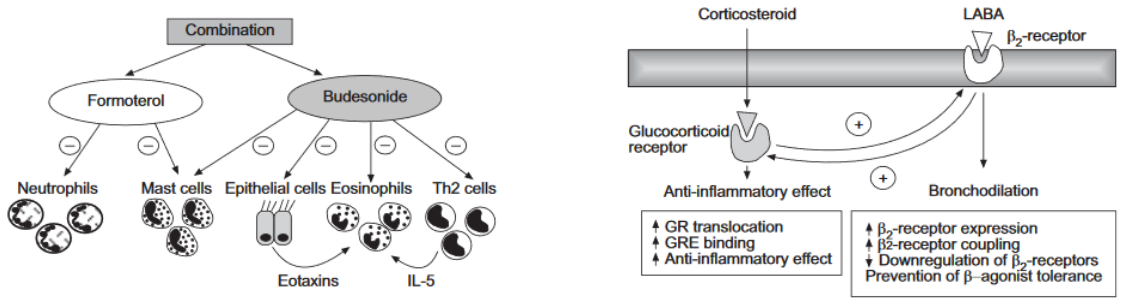
to first asthma exacerbation was prolonged in the group taking formoterol with a 13% reduction in the risk of a severe asthma exacerbation. [140]

These findings were summarised in Cochrane systematic review which concluded that 'in adults symptomatic on low to high doses of ICS monotherapy, the addition of a LABA at licensed doses reduces the rate of exacerbations requiring oral steroids, improves lung function and symptoms and modestly decreases use of rescue short-acting beta agonists'. [182]

1.9.5.3 Complementary action of inhaled corticosteroid and long acting beta agonist

A number of studies have investigated the pathophysiology that might explain the complementary action of ICS and LABA. [183,184] Formoterol not only has a bronchodilator action but also immune-modulatory actions in preventing airway oedema, mast cell release of bronchoconstrictors and neutrophil recruitment to the lung. [185–189] It is these characteristics that contribute to the role of the LABA in reducing asthma exacerbations.

LABAs can perform ligand independent activation of the glucocorticoid receptor [190] and increase the translocation of the glucocorticoid receptor to the nucleus. In turn this regulates gene transcription and inflammatory cell activity, suppressing release of the chemokines CXCL8 and CCL8 which are involved in eosinophil and neutrophil recruitment to the airway. [191] Corticosteroids reciprocally act to increase beta receptor expression in the airway smooth muscle. Thus, ICS and LABA have complementary intracellular interactions and effects on airway function. [44,192–194]



• Figure 8: Anti-inflammatory effects and interaction between corticosteroid (budesonide) and long-acting beta agonist (formoterol)

Reproduced with permission from Barnes, P. J. Scientific rationale for using a single inhaler for asthma control. Eur. Respir. J. 29, 587–595 (2007) [195]

1.9.5.4 Adjustable maintenance dosing

Given the efficacy of combination ICS/LABA therapy in improving asthma control and in reducing exacerbations, twice daily maintenance combination ICS/LABA therapy was adopted as a Step 3 treatment for those with asthma uncontrolled on regular ICS maintenance therapy. Concern subsequently grew that fixed dose treatment with ICS/LABA may result in a patient taking more medication than they needed, with the associated medication cost and risk of side effects when asthma was well-controlled and inadequate medication during an asthma exacerbation with the associated increased healthcare cost. [196,197]

Eight studies were published by authors in Europe and Canada investigating the efficacy and tolerability of ICS/fast-onset LABA (budesonide/formoterol) adjustable maintenance dosing (one to two inhalations twice daily stepping up to four inhalations twice daily as dictated by asthma symptoms and peak flow) as compared to fixed maintenance dosing (two inhalations twice daily). [196–203]

Three of these studies demonstrated that this regimen resulted in a reduced incidence of exacerbations and reduced the mean inhaled steroid dose per patient per day compared with the fixed dosing regimen. These findings were thought to be due to patients being able to increase their inhaled steroid treatment earlier in the course of an exacerbation than otherwise possible. The lack of efficacy seen in the five remaining studies was thought to be due to the short study duration of less than six months not being long enough to detect a change. Interestingly, half of the patients in the Canadian study did not increase their dose despite a deterioration in their asthma symptoms suggesting that a significant proportion of patients are not able to follow a plan and manage their disease in an adjustable fashion.[201]

1.9.5.5 ICS/fast-onset LABA use as a reliever – the maintenance and reliever therapy (MART) regimen

Over the past ten years there has been a growing body of evidence demonstrating the role of ICS/fast-onset LABA combination inhaler use for maintenance and relief of symptoms. [195] This addresses the problem of patients relying on their SABA when their asthma symptoms deteriorate. This approach is possible given the features of fast-onset LABAs described above.

The MART regimen has been found to be efficacious using budesonide/formoterol combination regimens in adults and children [204] using both Turbuhaler [70,205,206]and metered dose inhaler (MDI) devices[207,208], and using beclomethasone-formoterol in an MDI. [208] A recent meta-analysis of 16 randomised clinical trials, most of which recruited exacerbation-prone patients with poor asthma control or an exacerbation in the previous year, (N= 22748) concluded that the MART regimen

resulted in a reduced risk of asthma exacerbations compared with SABA reliever therapy in adults taking maintenance ICS/LABA with a relative risk of 0.68 (95% CI 0.58 to 0.80). [209]

Two key studies in this meta-analysis were the STAY and FACET studies. [210,211] The STAY study evaluated whether replacing the usual SABA reliever with a fast-onset ICS/LABA (budesonide/formoterol 80/4.5µg twice daily) combination inhaler would provide symptom relief and reduce asthma exacerbations. In this double blind, parallel-group study, of the 2760 subjects studied, those using the ICS/fast-onset LABA combination inhaler as both maintenance and reliever had improved lung function, fewer total exacerbations and a 45% reduction in risk of a severe exacerbation requiring medical intervention (hazard ratio, 0.55; 95% CI 0.44 to 0.67). This group also had lower exposure to oral steroids and reduced reliever medication use compared to those using either ICS/fast-onset LABA (budesonide/formoterol 80/4.5µg twice daily) with a SABA reliever (terbutaline 400µg) or high dose ICS (budesonide 320µg twice a day) as maintenance with a SABA (terbutaline 400µg) reliever. Of note, half of the severe exacerbations in the study were identified retrospectively due to an observed fall in peak flow. In 87% of cases, no medical review had been sought. Despite this, even when only severe exacerbations requiring medical review were analysed there was still a 50% reduction in the risk of a severe exacerbation in the group using ICS/fast-onset LABA as both maintenance and reliever with a longer time to repeat exacerbation suggesting a role in frequently exacerbating asthmatics. The STAY study is limited in its generalisability to clinical practice. It excluded patients with high baseline use of reliever medication and required patients to demonstrate 12% bronchodilator reversibility to be eligible for enrolment, which has poor sensitivity and specificity in asthma.[212] In addition, patients were enrolled on the basis of having asthma symptoms and a history of asthma exacerbations during the study run-in period, but patients randomised to use twice daily ICS/fast-onset LABA with a SABA reliever would have had a reduction in their ICS dose.

The worry might be that patients using this regimen over rely on and over use their reliever combination inhaler and receive an inappropriately large ICS and LABA dose just as some patients over rely on their SABA. [213,214] Reassuringly, in the STAY study, reliever use was lower in the combination inhaler group than in the groups using a SABA reliever (495 episodes of using the reliever more than four times a day in the combination inhaler group versus 1347 episodes in the ICS/LABA maintenance and SABA reliever group and 1196 episodes in the budesonide and SABA reliever group). In addition, 55% of days were reliever use free in the ICS/LABA maintenance and reliever group. The mean daily dose of budesonide in the budesonide/formoterol maintenance and reliever group was 240µg/day, compared with 640µg/day in the budesonide and terbutaline group, again suggesting that it is the timing of the increase in ICS rather than the total ICS dose which

contributes to the reduced severe exacerbation rate. Overall corticosteroid burden did not increase as there was a subsequent reduction in exacerbations and reduced oral corticosteroid exposure.

The FACET study demonstrated that there is an average period of between five and seven days before a severe exacerbation is recognised and treated with oral corticosteroids. Using ICS/LABA as a reliever allows an increase in anti-inflammatory therapy at the time of increased inflammation, which is causing increased symptoms, thereby reducing exacerbations. The SMILE study, in which patients were randomised to use a SABA, LABA or ICS/fast-onset LABA as a reliever confirmed that although formoterol is more effective than terbutaline in reducing severe exacerbations, a budesonide/formoterol combination reliever is even more effective, again confirming that at least part of the benefit from an ICS/fast-onset LABA reliever is due to additional ICS.

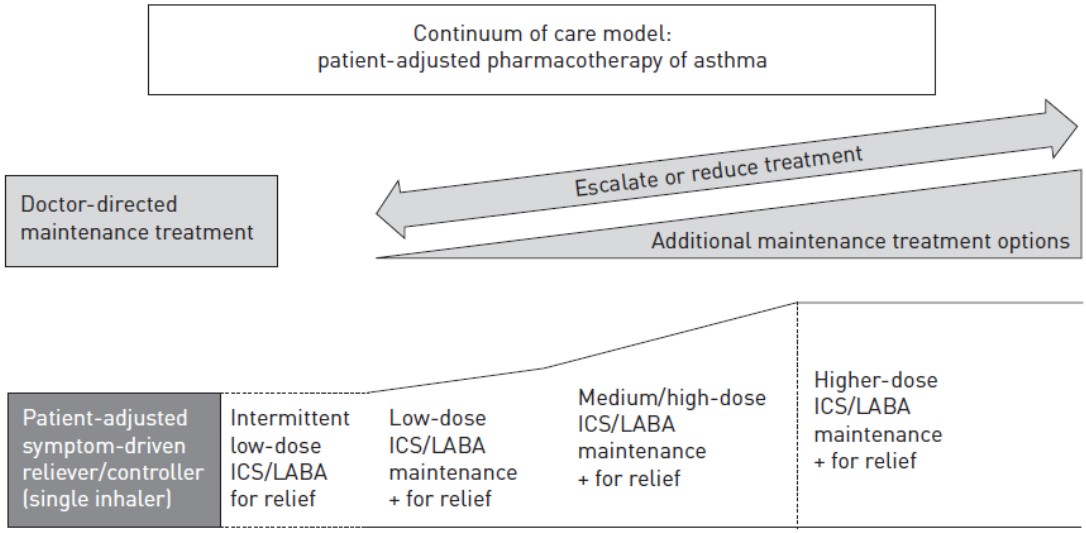
In summary, not only is the ICS/fast-onset LABA preventer and reliever combination regimen effective in reducing exacerbations, as inhaled corticosteroid is delivered alongside LABA as soon as the patient becomes aware of worsening symptoms and inflammation is worsening, it avoids unopposed SABA overuse[215–220] and is cost effective. [221,222] It is simpler than using separate maintenance and reliever inhalers without the need for complicated management plans on how to adjust maintenance doses. Given that the regimen is symptom guided, the number of days in which no ICS is taken are lower, there is less excessive unopposed use of beta agonist and the anti-inflammatory medication is titrated to need. [79,91,207]

Maintenance ICS/fast-onset LABA with an ICS/fast-onset LABA reliever is recommended for moderate and severe asthmatics at risk of exacerbations. [1] Entrenched practice persists however, and most patients continue to be prescribed SABA reliever therapy at these steps even if they exacerbate frequently. [223] The finding described above, namely that ICS/fast-onset LABA therapy is more efficacious than SABA as a reliever in patients taking regular maintenance ICS/LABA, raises the question of whether the same may be true in those who are not prescribed any regular maintenance therapy and equally those who are prescribed regular maintenance ICS with a SABA reliever who struggle to achieve satisfactory adherence.

1.9.5.6 Symptom guided ICS/fast-onset LABA

GINA steps 1 and 2 could be amalgamated, so that at the point of asthma diagnosis an ICS/fast-onset LABA inhaler, to be used only as required for the relief of symptoms, was initiated, with no regular maintenance component. Any increase in eosinophilic airway inflammation would be interpreted by the patient as an increase in asthma symptoms and need for a bronchodilator, with the ICS being delivered simultaneously. The INSPIRE study has shown us that this is what patients

want and do in practice. [80,84] If symptoms related to eosinophilic inflammation were persistent and clinical phenotype and endotype had been considered, the ICS/fast-onset LABA inhaler would be increased to regular and as needed use (the MART regimen). This approach would circumnavigate confusion over which inhaler to use when, over reliance on SABA and underuse of ICS, preserve patient autonomy and ensure that as the ICS is delivered some relief is obtained from the LABA, reinforcing the perception of benefit.



• Figure 9: Continuum of care model

Reproduced with permission from O'Byrne, P. M., Jenkins, C. & Bateman, E. D. The paradoxes of asthma management: Time for a new approach? Eur. Respir. J. 50, 1–8 (2017). [84]

'The first and most compelling reason for taking a treatment is that it causes a perceptible and important benefit, like relieving discomfort, increasing functional capacity or improving quality of life. The second reason is that it reduces the risk of harm in the future, like severe exacerbations of asthma or irreversible and limiting loss of function'.[224]

1.10 Summary

Where do the data we have reviewed above leave us? We can conclude that asthma is a heterogeneous inflammatory condition, with many patients suffering considerable ongoing morbidity (in terms of sub-optimal day to day asthma control and exacerbations that hasten lung function decline) and mortality. This is despite clear treatment escalation guidelines. Traditional regimens involving progressive addition of medications, including beta agonists and inhaled corticosteroids, are not adequately addressing the difficulties patients have in taking a regular medication for symptoms which are often only intermittent. The stepwise approach itself is contributing to this non-adherent behaviour. At Step 1 patients have the autonomy to interpret their level of disease control and take reliever therapy as they feel is indicated, whilst at higher asthma treatment steps, a maintenance treatment is recommended whatever the severity of symptoms, resulting in unintended over-reliance on SABA.

Over the last decade multiple strategies have been investigated to improve outcomes in mild and moderate 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 this group.

The outstanding question must be "is solely symptom guided, intermittent use of an inhaled corticosteroid safe and effective?" This question forms the basis of any future trial design to determine if a symptom only guided ICS/fast-onset LABA regimen is safe and effective in mild and moderate asthma.

2. CHAPTER TWO: LITERATURE SEARCH

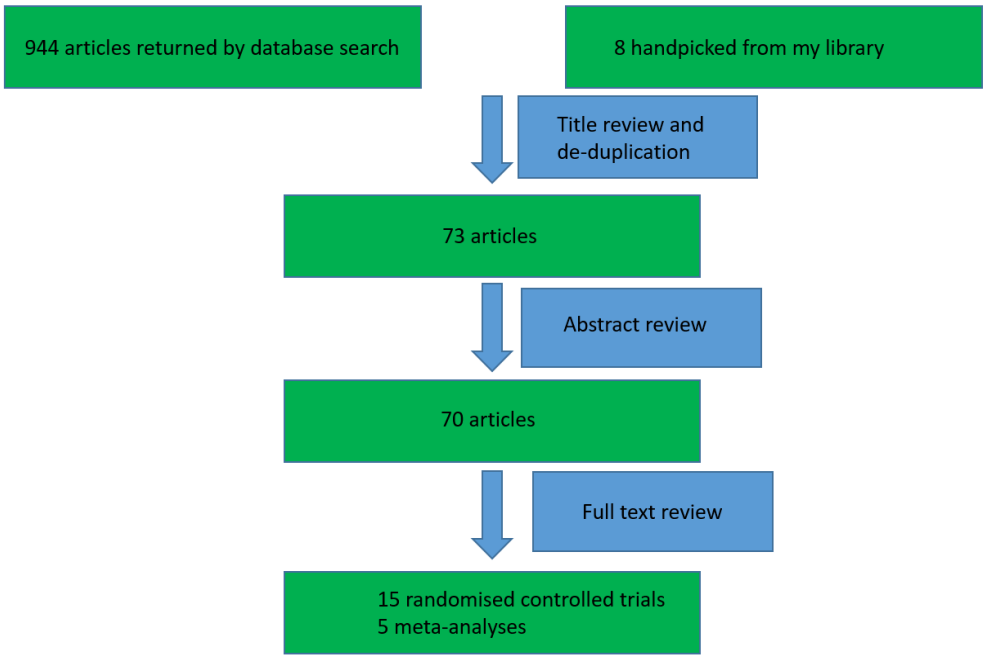
2.1 Is intermittent use of an inhaled corticosteroid safe and effective in asthma?

To address this question, a literature review to summarise all papers to date relating to intermittent use of an inhaled corticosteroid was performed on the 31st October 2017.

Ovid was used to search Medline (1948-present) and Embase (1947-present). The search terms used were:

Exp*antiasthmatic agent/ih (inhalational drug administration)
Exp * corticosteroid/ih (inhalational drug therapy)
corticosteroid therapy/ and (inhal and asthma*).tw
(inhaled corticosteroid* or steroid preventer*).ti
Or/1-4
(Prn or "pro-re-nata" or intermittent* or "as needed" or reliever).tw
Continuous or (regular adj2 dos*) or daily or maintenance or scheduled.tw
AND/5-7

Results were limited to Human. Results were not restricted by language. Titles and abstracts were screened for relevance and the full text of selected articles assessed. The results of the search are shown.



• Figure 10: PRISMA diagram for systematic review

The literature search was not limited to adults to avoid accidental omissions of relevant papers. Two studies will not be discussed as they looked at intermittent ICS use in pre-schooler wheeze which is considered to be a different entity to established asthma and there is limited evidence of benefit of ICS use in this group. [225,226] Two studies interested in pre-schooler wheeze, performed by Zeiger *et al* and Papi *et al* are included, as these studies were included in the Cochrane review of 2013. The randomised controlled trials and systematic reviews identified are outlined below.

Paper	Subjects	Intervention	Result	Problems
Boushey *et al*, 2005 (IMPACT study)	225 adults with mild asthma	Three treatment groups 1) Budesonide 200μg twice daily (BD) & placebo tablets BD 2) Placebo inhaler BD & zafirlukast 10mg tablets BD 3) Placebo inhaler BD & placebo tablets BD Patients were asked to take open-label budesonide (800μg BD) for ten days or prednisone (0.5mg per kilogram of body weight per day) for five days if their asthma symptoms worsened	• Intermittent ICS as effective as regular ICS in maintaining peak expiratory flow and preventing exacerbations • Regular ICS led to greater improvements in FEV1, bronchial hyper-responsiveness, sputum eosinophil counts, exhaled nitric oxide (FE_{NO}) & asthma control scores	• Generalisability limited by treatment of all patients with ten to 14 days of high dose oral prednisone on study entry
Haahtela *et al*, 2006 (SOMA study)	92 adult patients with mild asthma	Two treatment groups 1) Formoterol 4.5μg as required (PRN) 2) Budesonide/formoterol 160/4.5μg PRN	• Primary outcome, FE_{NO}, lower in ICS/fast-onset LABA group	• No regular ICS treatment comparator group
Papi *et al,* 2007 (BEST study)	455 adult patients with mild asthma	Four treatment groups 1) Placebo BD & beclomethasone/ albuterol 250/100μg PRN 2) Placebo BD & albuterol 100μg PRN 3) Beclomethasone 250μg BD & albuterol 100μg PRN 4) Beclomethasone/albuterol 250/100μg BD & albuterol 100μg PRN	• Symptom-driven as required use of combination ICS/SABA in a single inhaler achieved equivalent efficacy to regular ICS. • Morning peak flow was higher & number of exacerbations was lower in the intermittent group with a lower cumulative dose of ICS	• Peak flow primary outcome variable

Paper	Subjects	Intervention	Result	Problems
Turpeinen *et al*, 2008	176 children aged five to ten with mild asthma	Three treatment groups 1) Budesonide 400μg BD for two months, followed by budesonide 200μg BD for five months & budesonide 100μg BD from month seven to 18 (continuous group) 2) Budesonide taken in an identical manner to the first group for six months, followed by budesonide for exacerbations as needed for months seven to 18 (intermittent group) 3) Disodium cromoglycate (DSCG) 10mg TDS for 18 months & exacerbations treated with budesonide 400μg BD for two weeks	• There was no significant difference between the groups in morning peak flow at any time point • At 18 months, lung function did not differ between the groups • The number of asthma free days didn't differ between the continuous and intermittent group	• Children with moderate asthma also enrolled in study • Entirely Caucasian cohort
Papi *et al* 2009	276 children aged one to four with preschool wheeze	Three treatment groups 1) Beclomethasone 400μg BD & salbutamol 2500μg PRN 2) Placebo BD & beclomethasone/salbutamol 800/1600μg PRN 3) Placebo BD & salbutamol 2500μg PRN	• As compared with salbutamol PRN, the percentage of symptom-free days was higher with regular beclomethasone but not with PRN combination therapy	• Enrolled children with preschool wheeze rather than a diagnosis of asthma
Sposato *et al*, 2010	165 participants	Two treatment groups 1) 84 patients taking any ICS/LABA combination regularly 2) 81 patients taking any ICS/LABA combination intermittently as guided by symptoms	• At four years, the variation in decline in FEV1 was similar in both groups • Fall in the maximal mid expiratory flow (FEF25-75), a measure of small airway obstruction, was greater in intermittent group	• Retrospective study • Unequal baseline characteristics • ICS use was self-reported and therefore unreliable • 14 different medications used by participants

Paper	Subjects	Intervention	Result	Problems
Martinez *et al,* 2011 (TREXA study)	288 children and adolescents with mild asthma	Four treatment groups 1) Beclomethasone 40μg BD & beclomethasone 80μg & albuterol 180μg PRN (combined group) 2) Beclomethasone 40μg BD & placebo and albuterol 180μg PRN (daily group) 3) Placebo BD & beclomethasone 80 μg and albuterol 180μg PRN (rescue beclomethasone group) 4) Placebo BD & placebo and albuterol 180μg PRN (placebo group)	• Compared with placebo the frequency of exacerbations was lower in the daily, combined and rescue groups	• Separate ICS & SABA inhalers • Highly motivated group that may not represent general paediatric population • Very low dose of maintenance ICS used • No adults enrolled
Zeiger *et al,* 2011	278 children with preschool wheeze	Two treatment groups 1) Budesonide either intermittently (1mg BD for seven days at the onset of respiratory tract infection) 2) Budesonide 0.5mg OD Placebo controlled	• No difference in the frequency of exacerbations requiring oral corticosteroids seen between the groups	• Addresses preschool wheeze which is thought to be a different entity to asthma
Calhoun *et al*, 2012 (BASALT study)	342 adults with mild to moderate asthma	Three treatment groups: ICS dose changed as guided by 1) Physician assessment 2) Forced exhaled nitric oxide (FE_{NO}) (Biomarker adjusted) 3)Day to day asthma symptoms The physician assessment & biomarker based adjustment group had their ICS dose adjusted every six weeks. The symptom based adjustment group took ICS every time they used an albuterol reliever	• 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 the FE_{NO} guided, ICS-adjusted group for half the inhaled steroid dose	• Separate ICS & SABA inhalers • Included both mild & moderate asthmatics • The dose of ICS used was 6.25 times lower than in the BEST study • The study was designed to demonstrate superiority rather than equivalence

Paper	Subjects	Intervention	Result	Problems
Lazarinis *et al,* 2014	66 patients aged at least 12 years with verified mild exercise induced bronchoconstriction	Three treatment groups 1) Terbutaline 0.5mg PRN 2) Budesonide 400µg BD & terbutaline 0.5mg PRN 3) Budesonide/formoterol 200/6µg PRN	• Combination therapy PRN improved asthma control as assessed by ACQ5 & maximum post-exercise FEV1 by the same order of magnitude as regular budesonide with a 2.5 times lower budesonide dose	• Study only six weeks long • Small number of participants • Exercise induced symptoms only • No record of medication compliance • No measures of airway inflammation
Li *et al*, 2015 (Article in Chinese)	112 children with asthma	Two treatment groups 1) Salmeterol/fluticasone BD 2) Salmeterol/fluticasone PRN Doses not stated	• At 12 months the BD group had lower clinical symptom scores & higher peak flow & FEV1 when compared with the intermittent group ($P<0.05$)	• Study used salmeterol/fluticasone which is not licensed for reliever use as the LABA component, salmeterol is not adequately fast onset. • Not clear which reliever used by children in salmeterol/fluticasone BD group • The study was not randomised • Exacerbation rate was not an end point
Papi *et al*, 2015 (AIFASMA study)	866 adults with moderate asthma	Two treatment groups 1) Budesonide/formoterol 160/4.5µg PRN 2) Budesonide/formoterol 160/4.5µg BD and terbutaline 500µg PRN	• As-needed budesonide/formoterol was associated with a higher probability of treatment failure at one year (due to more nocturnal wakening) • Groups had similar efficacy in reducing severe exacerbations	• Comparison was to regular ICS/LABA rather than regular ICS • Significant missing secondary endpoint data • Study did not take any measures of airway inflammation (e.g. FE_{NO}) • No inhaler monitors used so compliance not recorded • No socio-economic assessment of direct or indirect costs recorded

Paper	Subjects	Intervention	Result	Problems
Beasley et al, 2016 (NovelSTART STUDY)	675 adults with mild asthma	Three treatment groups 1) Budesonide/formoterol maintenance 200/6µg PRN 2) Budesonide 200µg BD & albuterol 100µg PRN 3) Albuterol 100µg PRN	• Ongoing at time of literature review • Primary outcome annualised exacerbation rate per year • Use of electronic monitors to record inhaler use data • Measurement of T2 inflammatory profile markers • Open label	• Composite primary outcome
Fitzpatrick *et al*, 2016	300 children aged 12-59 months with asthma needing daily step 2 therapy to control symptoms	Three cross-over periods 1) Fluticasone 44µg BD 2) Montelukast 4mg OD 3) Fluticasone 44µg and albuterol sulfate 90µg PRN	• Probability of best response (a composite measure of asthma control which included time to exacerbation requiring systemic steroids & number of asthma control days) highest for daily ICS	• Asthma control days will always be lower in PRN ICS group as participant is waiting for symptoms to use medication • Separate inhalers used for ICS & SABA • Medication use self-reported • No washout phase between treatment periods – may have been some carryover effects • May have been impact of seasonal exacerbations • 25% drop out rate from study

Paper	Subjects	Intervention	Result	Problems
O'Byrne *et al* 2017	SYGMA 1; 3849 participants with mild asthma SYGMA 2; 4215 participants with mild asthma	The SYGMA 1 study: three groups 1) Placebo BD with budesonide/formoterol 200/6μg PRN 2) Placebo BD with terbutaline 250μg PRN 3) Budesonide 200μg BD with terbutaline 250μg PRN The SYGMA 2 study: three groups 1) Placebo BD 2) Budesonide/formoterol 200/6μg PRN 3) Budesonide 200μg BD and terbutaline 250μg PRN	• Ongoing at time of literature review • SYGMA 1 - composite outcome of asthma control (percentage of weeks of well-controlled asthma per patient). The primary objective is to demonstrate superiority of the ICS/fast-onset LABA as required regimen over terbutaline as required, a secondary objective is to demonstrate non-inferiority of ICS/fast-onset LABA to twice daily budesonide & PRN terbutaline • SYGMA 2 has severe exacerbation rate as its primary outcome	• Highly selected participant population therefore not reflective of real-world mild asthmatics • Placebo controlled, therefore real world benefits of intermittent regimen may be lost
Chauhan *et al*, 2013. Cochrane review, Intermittent versus daily ICS for persistent asthma	Boushey *et al* 2005 Martinez *et al* 2011 Papi *et al* 2007 Papi *et al* 2009 Turpeinen *et al* 2008 Zeiger *et al* 2011	N/A	• No significant difference in the number of moderate exacerbations in people using ICS intermittently versus every day • Equivalence could not be assumed given the lack of studies & wide confidence interval for the primary outcome measure of rate of severe exacerbations	• Ill-matched datasets • Inclusion of studies including children with preschool wheeze
Rodrigo *et al.* 2013	As per Chauhan *et al* Cochrane review plus Calhoun *et al* 2012	N/A	• 10% increase in asthma free days seen in the regular versus intermittent group • The daily ICS regimen was associated with higher total ICS dose	• The same concerns exist as they do for the Chauhan *et al* review

Paper	Subjects	Intervention	Result	Problems
Cochrane review, Intermittent ICS versus placebo for persistent asthma. Chong *et al* 2015	Martinez *et al,* 2011 Papi *et al.* 2007	N/A	• Risk of an asthma exacerbation requiring the use of oral corticosteroids was lower among school age children (OR 0.57 95% CI 0.29 to 1.12) & adults (OR 0.10 95% CI 0.01 to 1.95) who were randomised to take intermittent ICS versus placebo	• Only two studies in meta-analysis • Ill-matched datasets • Not all studies used ICS/LABA in a combination inhaler (Martinez)
Giofriddo *et al*, 2015	Meta-analysis of Papi *et al* 2007 & Martinez *et al* 2011	N/A	• The group found a statistically higher rate of asthma symptoms in groups using intermittent ICS	• Only two studies in meta-analysis • Not all studies used ICS/LABA in a combination inhaler (Martinez)
Wang *et al*, 2017	Systematic review & meta-analysis of intermittent ICS/LABA versus ICS. Papi *et al* 2007, Papi *et al* 2009, Martinez *et al* 2011, Fitzpatrick *et al* 2016	N/A	• Compared with regular ICS as-needed ICS/LABA saw higher risk of exacerbations (RR = 1.13, p=0.011) • Hazard ratio for time to first exacerbation was no different between the groups (HR 1.30, p=0.286) • Steroid exposure was two to five-fold lower in the intermittent ICS group	• Disparate populations compared. • Studies included disparate age groups & children with preschool wheeze • None of the studies were under real-world conditions • Not all studies used ICS/LABA in a combination inhaler (Martinez)

• Table 1: Summary of papers identified in literature review

2.1.1 Boushey *et al*, 2005

The IMPACT study 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. [54] The main outcome variables were morning peak flow and severe exacerbations requiring a course of prednisone.

225 adults with mild asthma were randomised to receive:

1) Budesonide 200μg twice a day and placebo tablets twice a day
2) Placebo inhaler twice a day and zafirlukast 10mg twice a day
3) Placebo inhaler twice a day and placebo tablets twice a day [54]

Patients were told to take open-label budesonide (800μg twice daily) for ten days or prednisone (0.5 mg per kilogram of body weight per day) for five days if their asthma symptoms worsened.

The regimen in which patients took a placebo inhaler and placebo tablet and intermittent corticosteroid if asthma symptoms worsened, had the same efficacy as regular budesonide treatment for outcomes including morning peak flow and rate of asthma exacerbations. Regular ICS led to greater improvements in FEV1, bronchial hyper-responsiveness, sputum eosinophil counts, exhaled nitric oxide (FE_{NO}) and asthma control scores.

The authors argued that although the intermittent ICS group had more days with symptoms, the symptom-utility index and quality of life scores suggested that this did not appreciably concern the study participants as the symptoms were so slight and infrequent. They also noted that the low-grade inflammation seen in the group using intermittent ICS was similar to that seen in patients with 'complete, sustained clinical remission of asthma in which no-one proposes daily controller treatment'.

The generalisability of the findings are limited by treatment of all patients with ten to 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. This is likely to have had a carry-over effect with a reduction in asthma symptoms and exacerbations seen. Also, the intermittent therapy group took ICS for only a mean of four days in this 12-month study suggesting that participants didn't take the study medication every time they had symptoms. No group received intermittent treatment with placebo or bronchodilators alone so it could not be concluded that intermittent treatment is better than use of rescue medication with bronchodilators.

2.1.2 Haahtela *et al*, 2006

This small study, the SOMO study, [227] looked at patients with mild, intermittent asthma and elevated FE_{NO} who were only taking SABA upon entry to the study. 92 patients were randomised to use either:

1) Formoterol 4.5 μg as required
2) Budesonide/formoterol 160/4.5 μg as required

The primary outcome, FE_{NO} was lower in the group receiving budesonide/formoterol as required, indicating better control of airway inflammation. A limitation of the SOMA trial was that there was no regular ICS treatment comparator group and the study was not powered to assess impact on asthma exacerbations.

2.1.3 Papi *et al*, 2007

This proof of concept study, the BEST study, investigated the efficacy of symptom driven ICS/SABA in a single inhaler. [228] The primary outcome was morning peak flow at week 23 and 24. Secondary outcomes included lung function, asthma control scores and percentage of days without asthma symptoms.

The study was a double-blind, placebo controlled, multicentre study. A study group of 455 patients aged between 18 and 65 with mild persistent asthma for at least six months and well-controlled on beclomethasone 250μg twice daily and albuterol as required were randomised to one of four treatment groups:

1) Placebo inhaler twice daily and as required combination ICS/SABA (beclomethasone/albuterol 250/100μg)
2) Placebo inhaler twice daily and as required albuterol 100μg
3) Beclomethasone 250 μg twice daily and as required albuterol 100μg
4) Beclomethasone/albuterol 250/100μg twice daily and as required albuterol 100μg

The participants were not provided with asthma self-management plans and were instructed to use their reliever treatments as guided by symptoms.

This study reported that in patients with mild asthma at baseline, the symptom-driven as required use of combination beclomethasone/albuterol in a single inhaler achieved equivalent efficacy to regular ICS. Morning peak flow was higher ($p=0.04$) and number of exacerbations was lower ($p=0.002$) in the intermittent ICS use group with a lower cumulative dose of 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 combined inhaler medication is not available in NZ or in other countries such as the US. The patients in the study had very mild asthma at baseline with FEV1 88% predicted, 32% on ICS at study entry, 51% symptom free days and rescue SABA use of 0.5 puffs/day. The study used peak flow as a primary outcome variable rather than a patient-centred outcome, such as exacerbations or asthma control. The study was not powered to assess severe exacerbations and follow-up was only six months, therefore the study wasn't able to assess any longer-term effects on the natural history of asthma of an intermittent regimen.

2.1.4 Turpeinen *et al*, 2008

This Finnish randomised controlled trial enrolled 176 children aged five to ten years old with newly detected asthma and randomised them to one of three treatment regimens: [229]

1) Budesonide 400μg twice daily for two months followed by 200μg twice daily for five months and 100μg twice daily from month seven to 18 (continuous group)
2) Budesonide in an identical manner to the first group for six months, followed by budesonide for exacerbations as needed for months seven to 18 (intermittent group)
3) Disodium cromoglycate (DSCG) 10mg three times a day for 18 months and exacerbations were treated with budesonide 400μg twice a day for two weeks

The primary end point of the study was peak flow, FEV1 and number of exacerbations. There was no significant difference between the groups in morning peak flow at any time point. The study found that at 18 months, lung function did not differ between the groups. Between seven and 18 months, patients in the continuous group had significantly fewer exacerbations (mean 0.97 (95% CI 0.70 to 1.34) compared with 1.69 (95% CI 1.31 to 2.18) in the intermittent group, and 1.58 (95% CI 1.20 to 2.08) in the DSCG group. The number of asthma free days didn't differ between the continuous and intermittent group.

The children in the study were all Caucasian so the results may not be generalisable to the non-Caucasian population. The authors highlight that children with moderate rather than mild persistent asthma were also included, as patients were being enrolled at the point of diagnosis and the severity of their asthma had not yet been quantified. The group concluded that in most children with mild asthma, the asthma can be well-controlled with proactive use of an ICS inhaler during an exacerbation after six months of regular ICS treatment, and that children exacerbating on an intermittent regimen at 12 months should be moved to regular maintenance therapy.

2.1.5 Papi *et al*, 2009

This study recruited 276 children with pre-school wheeze.[230] Only brief mention of it is made as the study was included in the Cochrane review paper published by Chauhan *et al* in 2013. There is not good evidence for the use of ICS in pre-school wheeze, and it is considered to be a separate pathophysiology to that of mild asthma. The primary end point of the study was the percentage of symptom-free days. This study randomised 276 symptomatic children with pre-school wheeze to one of three groups for a three-month period:

1) Beclomethasone 400μg twice daily plus salbutamol 2500μg as required
2) Placebo twice daily plus combination beclomethasone/salbutamol 800μg/1600μg as required
3) Placebo twice daily plus salbutamol 2500μg as required

As compared with as required salbutamol, the percentage of symptom-free days was higher with regular beclomethasone (61.0 ± 24.83) versus 69.6% ± 20.89; P=0.034) but not with the as required beclomethasone/salbutamol combination (64.9% ± 24.74).

This study is limited in its application due to the length of its follow-up and its enrolment of pre-school children with wheeze rather than a diagnosis of asthma.

2.1.6 Sposato *et al*, 2010

This was a retrospective study in which 165 patients were randomised into two groups: [231]

1) 84 patients taking ICS/LABA regularly
2) 81 patients taking ICS/LABA intermittently as guided by symptoms

The patients were divided into regular and intermittent groups based on self-reported ICS use over the year prior. Participants in the study used 14 different asthma medications. There were twice as many smokers in the intermittent group as the regular group. The primary outcome was FEV1 decline.

The study reported that after four years, the variation in decline in FEV1 was similar in both groups, (-276.97 ± 197.37ml: 95% CI -316.24 to -229.71) in the regular group and -317.65 ± 194.05: 95%CI -360.56 to -274.74) in the intermittent group. Fall in the maximal mid-expiratory flow (FEF25-75), a measure of small airway obstruction, was greater in the intermittent group. The numerous confounding factors described above significantly limit the validity of the study.

2.1.7 Martinez *et al*, 2011

The TREXA study [232] was an American, multi-centre, randomised, double-blind, placebo controlled trial in which 288 children and adolescents with at least a two year history of mild persistent asthma and current good asthma control were randomised to one of four treatment regimens:

1) Beclomethasone 40μg twice daily with beclomethasone 80μg and albuterol 180μg as reliever (combined group)
2) Beclomethasone 40μg twice daily with placebo and albuterol 180μg as a reliever (daily group)
3) Placebo twice daily with beclomethasone 80μg and albuterol 180μg as reliever (rescue beclomethasone group)
4) Placebo twice daily with placebo and albuterol 180μg as reliever (placebo group)

Participants took their randomised treatment for 44 weeks and had a four-week run in period during which they took beclomethasone 40μg twice daily.

The primary outcome was time to first exacerbation that required oral corticosteroids. The frequency of treatment failure, defined as a second course of prednisone within any six-month period was 23% (95% CI 14-43) in the placebo group, 5.6% (95% CI 1.6-14, p=0.012) in the combined group, 2.8% (0-10, p=0.009) in the daily group, and 8.5% (2-15, p=0.024) in the rescue group. Daily beclomethasone use decreased the risk for a first exacerbation by half whilst rescue beclomethasone use decreased this risk by a third compared to placebo. This effect did not reach significance.

The group concluded that inhaled corticosteroids as rescue medication with albuterol might be an effective step-down strategy for children with well-controlled, mild asthma as it is more effective than rescue albuterol use alone in the setting of poor adherence to regular ICS.

Limitations to the study's generalisability to the general paediatric asthma population include that the participants enrolled were a highly motivated group with greater than 75% adherence to the study medication. The study also used a low dose of maintenance beclomethasone, and the differences seen between the groups may have been greater if a higher maintenance dose had been chosen. Reliever beclomethasone and albuterol were in separate inhalers, risking non-compliance. It is likely that differences between the groups would have been more pronounced if a combination inhaler had been used.

2.1.8 Zeiger *et al*, 2011

In this study, young children without a diagnosis of asthma but at risk of asthma exacerbations and who had had an exacerbation in the previous year were recruited from sites around America. [233] A total of 278 children aged 12 to 53 months were randomised to receive either:

1) Budesonide intermittently (1mg twice daily for seven days at the onset of respiratory tract infection)
2) Budesonide 0.5mg once daily

Both of these were given with corresponding placebos.

The primary outcome was the frequency of exacerbations requiring oral corticosteroids.
No difference in the frequency of exacerbations was seen between the groups, with a rate per patient-year of 0.97 (95% CI 0.76 to 1.22) for the daily regimen and a rate of 0.95 (95% CI 0.75 to 1.20) for the intermittent group.

The study concluded that for a subset of children with recurrent wheezing and rare oral steroid use, intermittent high dose budesonide might be appropriate. Pre-schooler wheeze is considered a different entity to persistent asthma. Furthermore, the lack of a placebo control group weakens the study's value.

2.1.9 Calhoun *et al,* 2012

The BASALT study [234] was a randomised, placebo-controlled proof of concept study. In it, 342 adults with mild to moderate asthma, well-controlled on ICS, had their ICS treatment tailored in relation to three strategies:

1) Guided by physician assessment
2) Guided by forced exhaled nitric oxide (FE_{NO})
3) Guided by day to day asthma symptoms

Subjects in the physician-adjusted group took ICS twice daily, and the dose of the ICS was assessed and adjusted at six-weekly intervals. In the FE_{NO}-guided group, twice daily ICS dose was adjusted according to FE_{NO} every six weeks. Those in the symptom-guided group took two puffs of 40μg beclomethasone whenever they took two puffs of albuterol. Follow-up was relatively short at 36 weeks so no comment could be made on long term outcomes. The primary outcome was time to treatment failure.

The symptom-guided regimen was associated with a statistically non-significant 38% reduction in time to treatment failure, compared with physician-based adjustment. The symptom-driven approach resulted in a similar rate of exacerbations to the FE_{NO} guided ICS-adjusted group, however participants in the symptom-guided group took significantly less ICS than the other groups.

The patients in the study received closer surveillance than those followed up in general practice, and median adherence to treatment in the trial was 95%, much greater than would be seen in the clinical setting. The dose of ICS used was lower than that in other similar studies. The study was designed to demonstrate superiority rather than equivalence and must be interpreted accordingly. The patients enrolled in the study were mild asthmatics, well-controlled on ICS at baseline, which limits the generalisability and external validity of the results to less well-controlled patients. These patients were doing well on a physician-guided strategy prior to study entry and responded well to physician-guided care during the trial. Additionally, as the ICS and SABA in the symptom-guided group were provided in separate inhalers, the benefits of this approach may have been under-estimated.

2.1.10 Lazarinis *et al*, 2014

This small study was the first to assess the efficacy of symptom-guided use of ICS/fast-onset LABA therapy in exercise-induced mild asthma. [235] This AstraZeneca sponsored study was randomised, double-blind, double-dummy and six weeks in duration. A total of 66 participants aged over 12 with mild asthma, exercise induced symptoms and using a reliever medication up to four times per week with an FEV1 >80% predicted were enrolled. Participants were randomised to three groups:

1) Terbutaline 0.5mg as required
2) Budesonide 400μg twice daily and terbutaline 0.5mg as required
3) Budesonide/formoterol 200μg/6μg as required

The primary outcome was exercise-induced bronchoconstriction, as measured by post exercise FEV1, 24 hours after the last dose of study medication. The study found that budesonide/formoterol combination as required improved asthma control and post exercise FEV1 by the same order of magnitude as regular budesonide, with a two and a half times lower dose of budesonide.

This study had limitations in that it only ran for a six-week period, included only a small number of participants with only exercise-induced symptoms and did not record compliance with study medication.

2.1.11 Li *et al*, 2015

This small Chinese study published in Chinese enrolled 112 children diagnosed with asthma and randomised them to receive either: [236]

1) Salmeterol-fluticasone combination inhaler twice daily
2) Salmeterol-fluticasone combination inhaler as required

The primary outcome was 'clinical symptom scores' and FEV1. At six and 12 months of treatment the standard group had significantly increased FEV1 as compared to the intermittent group. It is not clear if this study was randomised. It is not clear what the regular group used as a reliever. Salmeterol/fluticasone combination has a slow time of onset and is therefore not licensed to use as a reliever inhaler in New Zealand.

2.1.12 Papi *et al*, 2015

This was the first study to address the efficacy of intermittent symptom-guided use of ICS in patients with moderate asthma. [237] It was investigator-initiated rather than pharmaceutical company sponsored. 866 adults aged 18 to 65 with stable, moderate persistent asthma were randomised to one of two groups:

1) Budesonide/formoterol 160/4.5μg as required
2) Budesonide/formoterol 160/4.5μg twice daily with terbutaline 500μg as required

The primary outcome was time to treatment failure which was a composite measure based on healthcare use, additional steroid use, high rescue medication use, nocturnal wakening and study withdrawal due to patient dissatisfaction or doctor concern. The as needed group was associated with a lower probability of patients having no treatment failure at one year (53.6% versus 64.0% (95% CI 3.2-17.4), with a shorter time to treatment failure largely due to nocturnal waking (82 patients in the as needed group versus 44 in the regular treatment group). The number of courses of oral steroids was similar in both groups which may be due to the higher drop-out rate in the regular group (34%) when compared with the as-required group (26%). This increased rate of drop-out would mean there were fewer patient-exposure years in which asthma exacerbations could occur.

The study had limitations, including that there was significant missing data for the secondary endpoints, FE_{NO} was not measured and frequency of medication use was not recorded using inhaler monitors.

In this study in patients with moderate, stable asthma, as required ICS/fast-onset LABA treatment was found to be less effective in maintaining asthma control but with similar efficacy in reducing severe exacerbations as compared to maintenance ICS/fast-onset LABA with SABA reliever therapy.

2.1.13 Beasley *et al* 2015

The NovelSTART study was ongoing at the time of this literature review. It is an Astra-Zeneca funded, investigator initiated open–label randomised controlled trial that investigated the intermittent use of budesonide/formoterol regimen in mild asthma. A total of 675 participants were recruited from sites around the world and randomised to one of three treatment regimens: [238]

1) Budesonide/formoterol 200/6μg as required
2) Budesonide 200μg twice daily with an albuterol reliever 200μg as required
3) Albuterol reliever 200μg only as required

Enrolled participants were on SABA only at baseline and therefore had mild asthma. Participant adherence and therefore inhaled corticosteroid intake was recorded using electronic monitors on all study inhalers. Participants had their T2 inflammatory profile (FeNO, eosinophils) recorded at baseline.

Limitations of the study include the composite primary outcome measure of annualised severe exacerbation rate per year defined as;

i) Worsening asthma resulting in urgent medical review (primary care visit, emergency department (ED) visit or hospital admission); and/or

ii) Worsening asthma, resulting in the use of systemic corticosteroids, such as prednisone, for any duration; and/or

iii) Worsening asthma resulting in a high beta agonist use episode, defined as more than 16 actuations of salbutamol or more than eight actuations of budesonide/formoterol within a 24-hour period.

2.1.14 Fitzpatrick *et al,* 2016

This American study recruited 300 children and following a run-in period of two to eight weeks determined by exacerbation history and current medication. Participants entered a randomised cross-over of three 16-week treatment periods.[239] The three treatments options were:

1) Fluticasone 44μg twice daily
2) Montelukast 4mg once daily
3) Fluticasone 44μg and albuterol sulfate 90μg as required

The primary outcome of the study was differential response to asthma medication based on a composite measure of asthma control. 74% of the children with data had a differential response (60 children had no differential response) with the best response being to daily ICS and predicted by allergen sensitisation and high blood eosinophils but not exacerbation history or gender.

The study had several limitations. The dropout rate for the study was high at 25% with a disproportionally high drop out of African-Americans. Medication use was self-reported without any use of electronic monitors, and separate inhalers were used to deliver ICS and SABA. There was no washout phase between treatment periods such that there may have been some carryover effects of one treatment onto the next. Most significantly, the primary outcome chosen, asthma control days, will always be poorer in the intermittent ICS group, as participants wait for symptoms to take the medication.

2.1.15 O'Byrne *et al,* 2017

The SYGMA programme [240] is an AstraZeneca-funded international programme and consists of two double-blind, 52-week, multicentre, parallel group trials in patients aged over 12 who would qualify for treatment with an ICS inhaler. The study was ongoing at the time of this literature search.

In SYGMA 1, 3750 participants will be randomised to receive either:

1) Placebo twice daily with budesonide/formoterol 200/6μg
2) Placebo twice daily with terbutaline 250μg as required
3) Budesonide 200μg twice daily with as-needed terbutaline 250μg

The primary objective of the study was to investigate superiority of the budesonide/formoterol as required regimen over terbutaline as required in terms of weeks with well-controlled asthma.

SYGMA 2 randomised 4114 patients to receive either:

1) Placebo twice daily and budesonide/formoterol 200/6μg as required or
2) Budesonide 200 μg twice daily and terbutaline 250μg as required

The primary outcome for the study was severe exacerbation rate. Positive aspects of these studies include their year-long duration of follow-up and the use of electronic monitors to record medication use. Inclusion criteria were tight, and patients had to demonstrate at least 12% reversibility in FEV1 following administration of 1mg terbutaline to be eligible for randomisation. Participants were excluded if they had more than a ten pack-year smoking history. As such, generalisability to the general practice population may be limited. As the study is placebo-controlled, the authors note that additional pragmatic open-label studies to evaluate natural patient behavior with an open-label regimen will be necessary in order that the results can be generalised to clinical practice. This is the role of the PRACTICAL study, and the focus of this thesis.

2.1.16 Chauhan *et al* Cochrane meta-analysis, 2013

This Cochrane review aimed to identify and analyse the parallel group trials comparing intermittent with daily ICS use in persistent asthma and analysed data from six studies: Boushey *et al*, Martinez *et al*, Papi *et al* 2007, Papi *et al* 2009, Turpeinen *et al* and Zeiger *et al*. [241]

Studies involving both adults and children with persistent asthma were included as well as studies including pre-school children at risk of asthma. Persistent asthma was not defined. Studies using ICS/SABA were included in the analyses but studies using ICS/LABA were not. The primary end point was the number of patients with a severe exacerbation defined as those requiring a course of oral steroids. The findings of this meta-analysis were not conclusive (risk ratio 1.07, 95% CI 0.87 to 1.32). Secondary outcomes included measures of asthma control, including SABA use, symptom-free days and exhaled nitric oxide. These favoured regular treatment. There were no significant differences in serious adverse events between the groups (relative risk 0.82, 95% CI 0.33 to 2.03). The authors concluded that equivalence could not be assumed given the lack of studies and wide confidence interval for the primary outcome measure.

There are four main concerns with the meta-analysis, which are largely due to comparisons that are drawn between ill matched datasets. The first concern is the decision to include studies involving pre-school age children at risk of asthma, as there is not good evidence for the use of ICS in preschool wheeze. Secondly, the dose of ICS used across the trials varied. Martinez *et al* and Zeiger *et al* used low daily doses of ICS, Papi *et al* used medium daily doses of ICS and Turpeinen *et al* started with a medium dose then tapered to a low dose. Thirdly, the definition of 'intermittent use' varied between the included studies. In three studies, intermittent ICS use comprised taking ICS and SABA in separate inhalers at the same time to treat asthma symptoms, while in three other studies intermittent ICS use consisted of a fixed dose of ICS being taken for seven to 14 days when suffering an asthma exacerbation. Comparison was therefore made between studies in which

patients would have gone for weeks to months without using ICS versus those receiving ICS more regularly. Fourthly, the run-in treatment in each of the studies was inconsistent. It varied from daily oral steroids and montelukast in one study to six months of daily ICS in another. In the studies involving pre-school children the run-in treatment varied between initiation with regular versus intermittent ICS. Turpeinen *et al* and Papi *et al* enrolled children with symptoms of asthma prior to starting treatment, whilst Martinez *et al* and Zeiger *et al* included children who had already been initiated on preventer inhalers and whose asthma was controlled during the run-in period. As such the Turpeinen *et al* and Papi *et al* studies were designed to determine if intermittent ICS is a suitable regimen for initiation of treatment in children with asthma, whilst the Martinez *et al* and Zeiger *et al* studies were designed to determine if intermittent ICS would be a suitable stepdown treatment for children whose asthma is well-controlled on a regular regimen.

2.1.17 Rodrigo *et al*, meta-analysis, 2013

This meta-analysis [242] drew on the same six studies as the Cochrane review described above, but also included the BASALT study published by Calhoun *et al*.

The conclusions drawn were much the same, with a 10% increase in asthma-free days seen in the regular versus intermittent group. The daily ICS regimen was associated with greater ICS dose. The same concerns exist for the Rodrigo *et al* meta-analysis as they do for the Chauhan review.

2.1.18 Gionfriddo *et al*, meta-analysis, 2015

This systematic review and meta-analysis examined the effect of stepping down from scheduled to as required ICS in patients with stable asthma. [243] It identified two studies for analysis, Papi *et al,* 2007 and Martinez *et al*.

The meta-analysis included only studies in patients with a diagnosis of stable asthma, which was defined as a four-week period without an asthma exacerbation prior to enrolment. The relative risk of an exacerbation on stepping down from regular to as needed ICS was 1.32 (95% CI 0.8 to 2.16, p= 0.27) and those that remained on regular ICS had more symptom-free days (mean difference 0.26 (95% CI 0.02 to 0.49, p= 0.03). This meta-analysis was limited due to the small number of included trials and its heterogeneous population. The average age of participants in the Martinez *et al* study was ten, and in the Papi *et al,* 2007 study 37.

2.1.19 Chong J *et al*, Cochrane meta-analysis, 2015

This meta-analysis of six trials compared intermittent ICS use at the start of a deterioration in asthma symptoms with placebo treatment in adults and children with mild asthma and pre-school children with intermittent wheeze. [244] In an analysis of the two randomised controlled trials that did not include pre-school age children with intermittent wheeze (Martinez *et al,* 2011 and Papi *et al*. 2007), the risk of an asthma exacerbation requiring the use of oral corticosteroids was lower among school age children (odds ratio 0.57, 95% CI 0.29 to 1.12) and adults (odds ratio 0.10 95% CI 0.01 to 1.95) who were randomised to take intermittent ICS versus placebo. When the data from the two trials were combined, the odds ratio of having an asthma exacerbation that required a course of steroids for people taking intermittent ICS was half that of the placebo group (odds ratio 0.50, 95% CI 0.26 to 0.94). The same concerns and limitations exist for this meta-analysis as for the Chauhan *et al* and Gionfriddo *et al* meta-analyses.

2.1.20 Wang *et al,* systematic review and meta-analysis, 2017

This was a systematic review and meta-analysis of as-needed ICS/fast-onset LABA versus regular ICS, and as-needed LABA versus as-needed ICS/fast-onset LABA. [245] Six studies and a total of 1300 participants were included. The analysis of as-needed ICS/fast-onset LABA versus regular ICS included Papi *et al* 2007, Papi *et al* 2009, Martinez *et al* 2011 and Fitzpatrick *et al* 2016.

Compared with regular ICS, as-needed ICS/fast-onset LABA saw a higher risk of exacerbations (relative risk 1.13, p=0.011). The hazard ratio for time to first exacerbation was no different between the groups (hazard ratio 1.30, p=0.286). Steroid exposure was two to five times lower in the as-needed ICS/fast-onset LABA group. The studies included in the meta-analysis were disparate in baseline characteristics including by age group and diagnosis of pre-schooler wheeze rather than asthma. None of the included studies were under real-world conditions.

2.2 Summary

In summary, ICS taken regularly reduces the risk of exacerbations in patients with asthma, but in practice adherence is poor and the burden of disease from exacerbations is substantial. This literature review has demonstrated that the symptom guided, intermittent use of ICS is safe in a mild asthma population. Whilst acknowledging the limitations of the studies performed to date in this area, the largest meta-analysis of intermittent ICS use, published by Chauhan and colleagues, found no significant difference in the number of moderate exacerbations in people using ICS intermittently versus every day and no significant difference in adverse effects. With regard to efficacy, there remains insufficient evidence to conclude that the two regimens are equivalent. The studies reviewed here suggest that daily ICS use results in slightly better asthma control, improved lung function and fewer days with symptoms as compared to intermittent ICS use.

The scientific rationale and patient behaviour discussed earlier in this thesis would suggest that combining ICS and fast-onset beta agonist in a single combination inhaler for symptom guided intermittent use would reduce the burden of disease from exacerbations for many patients who struggle with adherence to a maintenance ICS regimen, and who in response to a worsening in asthma increase their SABA without increasing their ICS. Combining ICS and fast-onset beta agonist into one inhaler for symptom guided use would have the advantage of improving adherence to ICS whilst avoiding the unopposed beta agonist use which, as described earlier, increases future exacerbation risk and mortality.

Four key studies identified in this literature review would support the as-needed combination ICS/fast-onset beta agonist approach. The BEST study reported that combination beclomethasone/salbutamol (ICS/SABA) reliever therapy had similar efficacy to maintenance beclomethasone plus salbutamol reliever therapy in reducing exacerbation risk, and was superior to salbutamol reliever therapy. The BASALT study reported that ICS/SABA reliever therapy in separate inhalers resulted in a statistically non-significant reduction in time to treatment failure compared to maintenance ICS. The SOMA study demonstrated better control of airway inflammation with ICS/LABA reliever therapy compared to LABA reliever therapy. Finally, the AIFASMA study reported that budesonide/formoterol reliever monotherapy was inferior to regular budesonide/formoterol plus as-needed SABA for the outcome of treatment failure but no different for severe exacerbations in patients with moderate asthma.

As described earlier, this approach is also supported by findings from MART randomised controlled trials comparing ICS/formoterol reliever with SABA reliever in adults with moderate

and severe asthma taking maintenance ICS/LABA therapy. A meta-analysis reported that the use of ICS/formoterol as the reliever reduced the risk of asthma exacerbations compared with SABA reliever therapy.

Gaps in the literature remain. The two SYGMA studies, ongoing at the time of the literature review are pharmaceutical company funded with inclusion criteria that will exclude patients with the co-morbidities that are seen in general practice. Both are placebo controlled and given this, patient behaviour will not reflect that seen in the real world. Neither the NovelSTART nor the SYGMA studies are recruiting patients with moderate asthma. As such, there is no independently funded, open-label study comparing ICS/formoterol reliever therapy with maintenance ICS plus SABA reliever therapy, the traditional standard of care, in adults with mild to moderate asthma in the real-world setting.

Review of the studies above gives clear direction as to the primary and secondary questions that need to be answered and which I will proceed to address in this thesis.

The primary question is what is the efficacy of an ICS/fast-onset LABA reliever therapy regimen as compared with ICS maintenance and SABA reliever in adult patients with mild and moderate asthma?

Secondary questions include; what is the safety of an ICS/fast-onset LABA reliever therapy regimen compared with ICS maintenance and SABA reliever? Do baseline clinical characteristics such as smoking status and history of exacerbations predict a preferential response to treatment?

A clear, clinically relevant primary efficacy outcome supported by guidelines would be exacerbation rate. Additional, clinically relevant secondary efficacy outcomes would include day to day asthma control and markers of airway inflammation and obstruction (FEV1 and FE_{NO}).

Safety could be assessed through report of both adverse events and withdrawals from the study due to treatment failure. Careful clinical phenotyping of patients, using type 2 inflammatory status, smoking status and history of severe exacerbations would allow analysis of whether subgroups of patients preferentially respond to an intermittent ICS regimen.

The PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist (PRACTICAL) study, was designed to summarily address the question of

whether intermittent symptom driven use of an ICS/fast-onset LABA combination inhaler is safe and effective.

3. CHAPTER 3: PRACTICAL STUDY METHODS

3.1 Study overview

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

1) Budesonide/formoterol Turbuhaler taken as required for relief of symptoms (ICS/fast-onset LABA reliever therapy)
2) Budesonide Turbuhaler as maintenance and terbutaline Turbuhaler as required for relief of symptoms (ICS maintenance and SABA reliever therapy)

A total of 890 adult patients with asthma in whom ICS maintenance and SABA reliever therapy is recommended were recruited from sites throughout New Zealand.

3.2 Study hypothesis

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

3.3 Primary objective

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.

3.4 Secondary objectives

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 characteristics such as reported T2 inflammatory profile, smoking status, history of severe exacerbations and ethnicity predict preferential response to randomised treatments

3.5 Study duration

Participants were seen for six appointments at week 0, 4, 16, 28, 40 and 52. There was a visit window of five days either side of their visit due date within which visits were scheduled to occur. In some cases, at the investigator's discretion, visits were held early or postponed and the visit window was extended. An extra unscheduled visit was arranged if a participant had lost their medication or was concerned that it was running low.

3.6 Interventions

Participants were randomised in equal proportions to one of two treatments:

1) Budesonide/formoterol Turbuhaler 200/6μg, one actuation as required for relief of symptoms
2) Budesonide Turbuhaler 200μg, one actuation twice daily and terbutaline Turbuhaler 250μg, two actuations as required for relief of symptoms

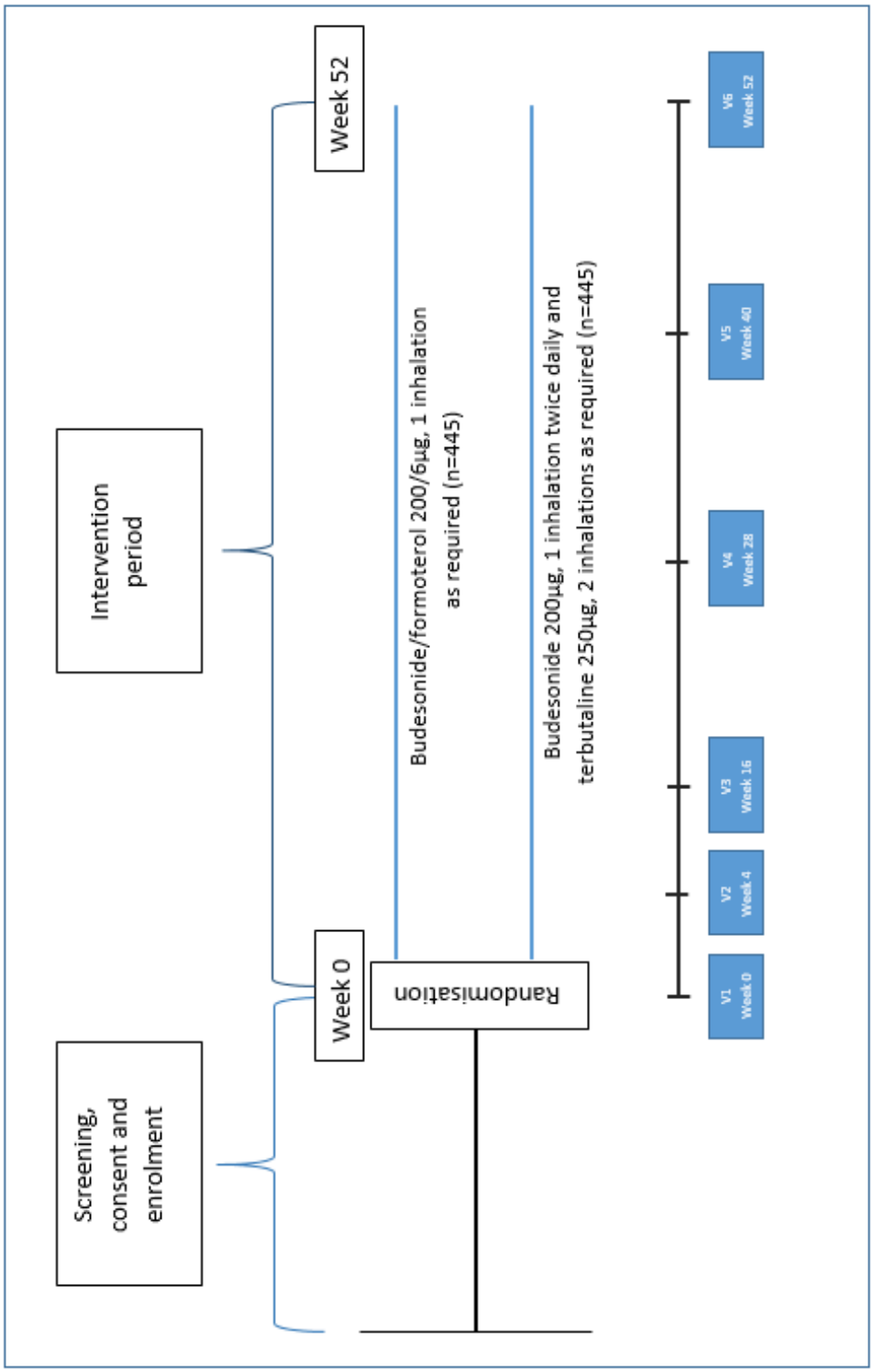
Budesonide Turbuhaler one actuation twice daily is considered to be the standard of care. There is no SABA only arm in the study. This is because for patients with mild asthma already on ICS, this would be an unjustified step down in treatment associated with the risk that their asthma would be less well-controlled.

The doses of budesonide used are based on its dose-response relationship in asthma and are consistent with consensus guidelines. [73,161] Budesonide 400μg/day achieves around 80-90% of the maximum obtainable efficacy for all major outcome measures including severe exacerbations.[161] In the initiation of ICS therapy there is no greater efficacy achieved with doses of budesonide >400μg/day[246.] For this reason consensus guidelines recommend that ICS therapy is initiated with a dose of budesonide of 400μg/day or equivalent. [247] The dose of budesonide/formoterol 200/6μg one inhalation as required for symptom relief was chosen as this is one of the doses recommended in the Single combination ICS/LABA inhaler for Maintenance And Reliever Therapy (SMART) regimen. [214] The 250μg terbutaline dose, taken two inhalations when required for relief of symptoms, was chosen as this is the recommended dose for use in New Zealand. [247]

Participants were randomised, stratified by site and by baseline ICS treatment with a block size of eight. A computer-generated randomisation number sequence was created by the blinded study statistician. The electronic case report form (eCRF) system concealed the allocations and released a participant's randomisation outcome at the time of randomisation. Study staff did not have access to the randomisation schedule.

Sites were responsible for documenting whether potentially eligible participants were excluded and why on a screening log. Potentially eligible participants were allocated an enrolment number (sequential number at that site prefaced with the letter E and the designated site number). When a participant was randomised the eCRF allocated a randomisation number to each participant (sequential number at that site prefaced with the letter R and the designated site number). Investigators allocated study medication to each participant based on their randomisation outcome. The investigator recorded the randomisation number on each dispensed inhaler. If a participant withdrew from the study their randomisation number was not re-used.

There was no blinding to allocated intervention in this study. Study investigators, study staff and the participant were aware of the treatment to which the participant had been allocated. The study was open label in order to maintain the potential real world advantage of the ICS/LABA reliever therapy regimen, which is the use of a single medication as required with no need for regular inhaler use. A blinded study would have required additional, regular placebo inhalers to be taken by the ICS/LABA reliever therapy group, and this real-world advantage would have been lost.



• Figure 11: Overview of study design

3.7 Primary outcome variable

The primary outcome variable of the study was the rate of severe exacerbations per patient per year. This outcome measure was chosen because it is a clinically relevant outcome and one recommended in the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement. [2]

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

a) The use of systemic corticosteroids for at least three days because of asthma, or
b) Hospitalisation or emergency department (ED) visit because of asthma, requiring systemic corticosteroids

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

3.8 Secondary outcome variables

1) To compare the safety of the ICS/fast-acting LABA reliever therapy regimen with the ICS maintenance and SABA reliever therapy regimen.
2) To determine whether baseline clinical characteristics such as Th2 profile (eosinophils, baseline FENO), smoking status, history of severe exacerbations and ethnicity predict preferential response to randomised treatments.

Clinical outcomes included rate of asthma exacerbations per patient per year defined as worsening asthma resulting in unplanned medical review (primary care, ED, hospital admission) and/or worsening asthma resulting in use of systemic corticosteroids for any duration. Additional clinical outcomes included time to first severe exacerbation of asthma, time to first exacerbation of asthma, the proportion of severe exacerbations defined by each of the above criteria, the proportion of participants with at least one severe exacerbation, ACQ-5, on-treatment FEV1 (i.e. without withholding bronchodilator medication), on-treatment FEV_1 percentage predicted, FE_{NO}, adverse events and serious adverse events. Also reported was the proportion of participants withdrawn and the reason and the proportion of participants withdrawn due to treatment failure. Treatment failure was defined as withdrawal from the study due to uncontrolled asthma resulting in safety concerns as judged by the investigator or an increase in asthma treatment by the patient's healthcare provider for more than 14 consecutive days.

3.9 Inclusion Criteria

1) Adults aged 18 to 75 years
2) Self-report of a doctor's diagnosis of asthma
3) a. Not used ICS in the 12 weeks prior to entry into the study AND
   i. Asthma symptoms or need for SABA ≥ two occasions in the last four weeks, or
   ii. Waking due to asthma at least once in the last four weeks, or
   iii. 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); ≤800μg/day budesonide; ≤1,000μg/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)
4) Willing and able to give informed consent for participation in the trial
5) In the investigator's opinion, able and willing to comply with all trial requirements
6) Willing to allow their GP (and specialist if appropriate) to be notified of participation in the trial

These inclusion criteria were chosen as they identify a real-world adult population of mild asthmatics whom 2014 GINA guidelines, current at the time the study was designed, recommended should receive ICS maintenance and SABA reliever therapy. There are no FEV1 reversibility inclusion criteria, ensuring that the study has good external validity and is representative of the mild asthma population treated by general practitioners. [248] Given that participants could have had well-controlled asthma while taking as much as 800μg budesonide or 500μg fluticasone, the population recruited represented those with mild-moderate asthma.

In the past four 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: GINA level of asthma symptom control

Assessment	Calculation
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 Poor adherence is less than or equal to 80%

• Table 3: Assessment of adherence

3.10 Exclusion criteria

1) Self-reported use of LABA, leukotriene receptor antagonist, theophylline or anticholinergic agent as maintenance therapy in the 12 weeks before potential study entry (nasal corticosteroid therapy is permitted)
2) Self-reported past admission to the Intensive Care Unit (ICU) with life-threatening asthma (representing patients at highest risk of adverse asthma outcomes)
3) Self-reported treatment with oral prednisone or other systemic corticosteroids in the six weeks before potential study entry (representing recent unstable asthma)
4) A home supply of prednisone for use in worsening asthma, as part of a current asthma plan
5) Self-reported diagnosis of COPD, bronchiectasis or interstitial lung disease
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
7) Self-reported current pregnancy or breast feeding at the time of enrolment or planned pregnancy within the study period
8) Unwilling or unable to switch from current asthma treatment regimen
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)

The exclusion criteria chosen ensured that patients who had had recent unstable asthma and those at highest risk of adverse asthma outcomes and should therefore be on a personalized asthma management plan were not enrolled. They also ensured that none of the participants had a step down in treatment at the point of study enrolment. The smoking criteria ensured that participants who had undiagnosed COPD, for which the treatment algorithm may be different, were not enrolled. Participants with a home supply of prednisone were excluded, as this could have affected the primary outcome of the study. Compared to other studies, the exclusion criteria around co-morbidity were minimal and unless a co-morbidity was likely to impact on the participant's safety or the study's feasibility, the participant was eligible.

3.11 Study Sites

The trial was conducted at 15 sites around New Zealand. These included six general practices; Henderson, Greenhithe, Team Medical, Coastal Medical Rooms and Waikanae Medical Centre and South Pacific, seven medical research institutes; P3 research, Optimal Clinical Trials, Lakeland, Papamoa Pines, Clinical Horizons, Southern Clinical Trials, RMC research and one hospital site, the Medical Research Institute of New Zealand (MRINZ), which also operated out of an after-hours medical centre. Participants were recruited to the study from each centre's patient database and through advertising using ethics-approved material in the local community. For the six GP practices, study visits were scheduled separately to usual clinical care.

To facilitate participant recruitment in the Wellington region, I approached 45 local GP practices who agreed to support the research, helped the practices to send 17,000 letters to their patients with asthma and fielded phone calls from 1826 people keen to learn more about the study.

Medical Research Institute of New Zealand	Mathew Williams, Jenny Sparks, Daniela Hall, Christina Baggott, Denise Fabian, Alison Pritchard, Saras Mane, Donah Sabbagh, Karen Oldfield, Irene Braithwaite, John Martindale, Allie Eathorne, Tony Mellon, Alice McDouall, James Fingleton, Richard Beasley
Optimal Clinical Trials	Barney Montgomery
South Pacific Clinical Trials	Edward Watson, Tina Mullard, Tyrone Tranquilino
Henderson Medical Centre	Rodney Marks, Andy Bass, Hank Zhang
Greenhithe	Nick Gailer, Jan Van Zuilen
Team Medical	Brent Krivan, Cheryl Robertson
Coastal Medical	Malcolm Dyer, Chris Jasinski
Waikanae Medical Centre	Dermot O'Connor, Anne-Christine Poracchia
Lakeland	Mike Williams
Papamoa Pines	Davitt Sheahan
Clinical Horizons	Andrew Corin, Colin Helm
P3 Medical Research	Dean Quinn, Stella Moon
Southern Clinical Trials	Rachel Harris, John Richmond, Gloria Ward
RMC Research	Jim Reid

Three of the GP sites had not previously been involved in a clinical trial. A rigorous site approval process was put in place to ensure that each site was set up prior to the 'green light' for recruitment

being given. Each site had to confirm locality authorisation and Maori consultation, have signed a contract with MRINZ and have insurance provision and indemnity in place for site staff. The sites had to have a contract with the local laboratory for full blood count sample processing and have appropriate storage facilities and temperature monitoring for the study drug. All PRACTICAL team members at each site had to demonstrate that they had been trained on the electronic case report form and the principal investigator had to have reviewed the protocol and signed off the study drug data sheets and provided delegated staffs' curriculum vitae prior to approval for recruitment being given.

I performed the site initiation visits (SIV) at each site, each one taking around six hours. This included a presentation to the site staff on the study background and rationale, an overview of the protocol objectives, inclusion and exclusion criteria, procedures, inhaler technique training and safety reporting. All the staff performing study specific procedures had to have up to date Good Clinical Practice (GCP) certificates, and at the SIV an overview of GCP was given. Hands-on training on the spirometer and FE_{NO} machines was performed. An introduction to the electronic case report form was presented and each member of the site team had the chance to review the process of randomising participants and data entry. Thereafter there was an open line of communication between me and the site staff, and I was able to offer trouble-shooting advice in real-time.

I wrote a data completion manual and study reference manual and this was issued to each site in order to support them in performing the study as per the protocol, and same day support via phone and email was offered to each site.

I wrote monthly study newsletters to keep the site investigators informed of the study's progress and any disseminate any protocol updates or issues.

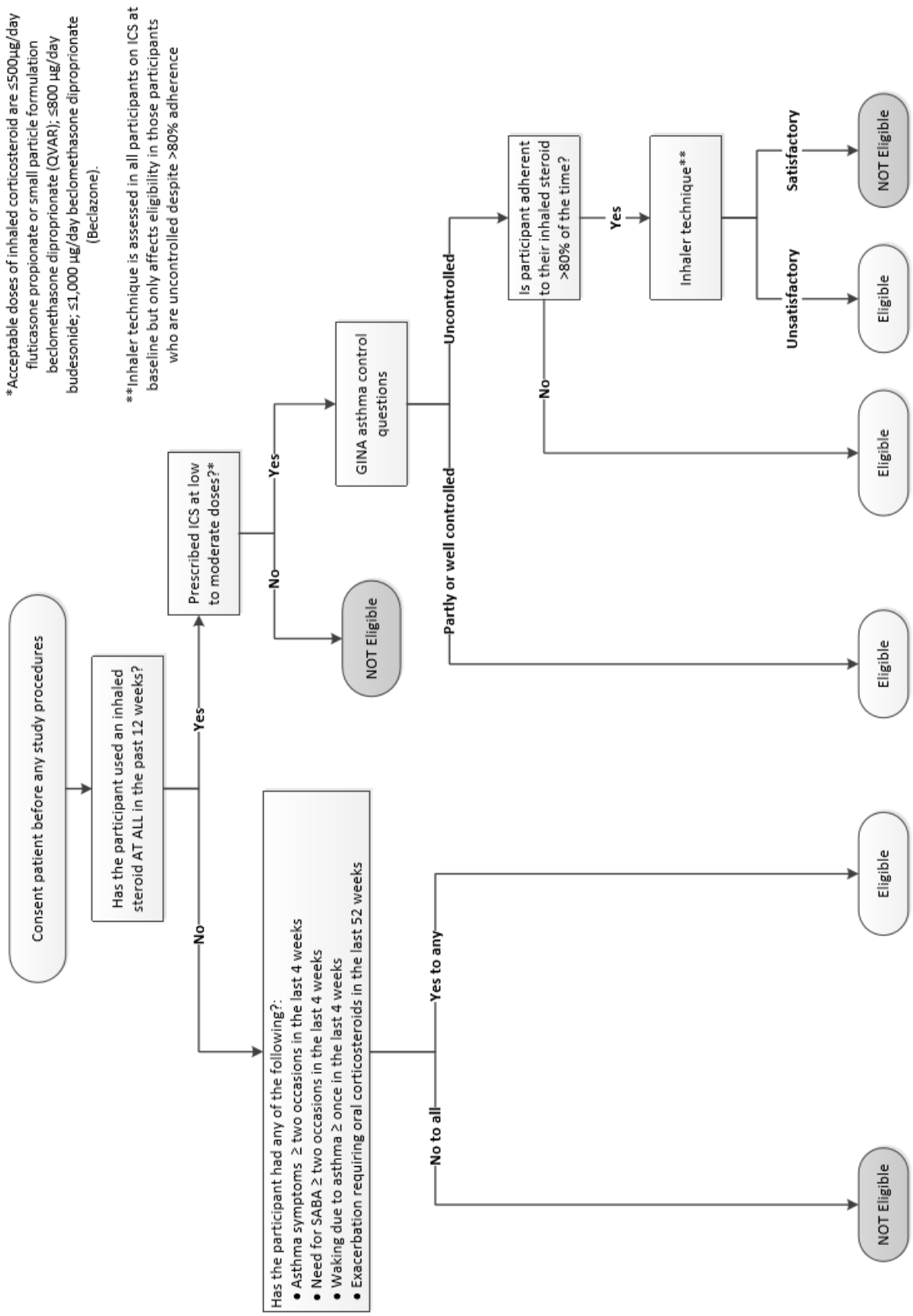
3.12 Visit overview and procedures

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
Written informed consent	●							
Inclusion/exclusion criteria check	●							
ACQ-5		●	●	●	●	●	●	
Medical history & demographics		●						
Weight and height		●						
FE_{NO}		●		●			●	
Spirometry		●		●			●	
Blood test for full blood count		●						
Randomisation		●						
Study ICS inhaler technique assessment			●	●	●	●	●	
Participant education & issuing of study inhalers		●	●	●	●	●		As required
Issue written asthma action plan and other written information		●						
Inform GP of study enrolment		●						
Review: - Exacerbations - AEs - SAEs - Medication changes			●	●	●	●	●	●
If participant is to be withdrawn, documentation of cause and notification to GP			●	●	●	●	●	●
Inform GP of study completion							●	

• Table 4: Overview of visits

3.12.1 Initial screen

Potentially eligible participants were asked initial screening questions over the phone relating to the inclusion and exclusion criteria previously mentioned. If the person was considered eligible, they were emailed or posted a copy of the participant information sheet (PIS, see Appendix) and if they were keen to be involved a date and time was arranged for Visit 1. Participants continued to take their usual inhaled therapy prior this visit and were asked to bring the inhalers and any additional medication they had used in the past three months to the appointment. The flow chart below was used by sites to make the process of confirming eligibility more straightforward.



• Figure 12: Enrolment flowchart

3.12.1.1 Consent

Before any study specific procedures were performed, written informed consent was taken from each participant as per GCP guidelines (see Appendix). It was made clear to each participant that they remained under the care of their usual GP for the duration of the study. Each participant was provided with an asthma management plan which contained details of the study treatment and contact details for the study investigator.

3.12.1.2 Questionnaires

The participant was asked to read and fill in each questionnaire without intervention by the investigator. Where this was not possible the investigator read and/or recorded answers for the participant, and it was documented that this took place.

3.12.1.3 Asthma control questionnaire ACQ-5

The asthma control questionnaire 5 (ACQ-5) was administered before either history taking or spirometry to reduce the chance that these interventions could influence the participant's perception of their asthma control and affect the ACQ-5 result. The ACQ is the mean of five questions about asthma symptoms during the previous week, each scored on a seven-point scale between zero (no impairment) and six (maximum impairment). A 0.5-unit change represents the minimal clinically important difference. A score of 1.0 represents the crossover point between well-controlled asthma and not-well-controlled asthma. The ACQ-5 questionnaire was chosen as it is a validated measure of both adequacy and change in asthma control both within and between participants. [53,78,249–251] The questionnaire was in a paper format. [252] The ACQ-5 questionnaire was completed at every visit. In administering this questionnaire multiple times over the course of the trial, an individual's variation in level of control and the size and significance of any response to treatment could be assessed.

3.12.2 Medical history and demographics

At Visit 1 detailed medical history and demographics were also collected. This information ensured that the participant was eligible for the study and supplied data necessary for subsequent sensitivity analysis. Information collected included:

- Date of birth, age and sex
- Smoking history: status and pack years
- Asthma history: age of diagnosis, current use of an asthma action plan and whether it was with or without peak flow measurement, GINA level of asthma control, whether currently prescribed ICS, which product and at what daily dose, assessment of ICS

adherence compared to prescription, assessment of ICS inhaler technique, SABA use in the past four weeks, number of courses of systemic corticosteroids for asthma in the last year and number of days per course, number of emergency department (ED) visits for asthma in the last year and for each visit whether a systemic corticosteroid was administered, number of hospital admissions for asthma in the last year, number of severe exacerbations (as per ATS/ERS criteria) of asthma in the past year

- Other medical conditions and medications
- Weight and height for calculation of spirometry predicted values

3.12.3 Randomisation

An electronic case report form (eCRF) was used to randomise subjects into the study, dispense and track medications and enable data entry for each patient. After they had received training, study staff were given access to the eCRF system and were asked to complete data entry within a 24-hour period following a study visit.

3.12.4 Measures of lung function and type 2 immune response

Forced exhaled nitric oxide (FE_{NO}), a marker of eosinophilic T2 lung inflammation, was performed prior to spirometry [253,254] and collected at the first, third and final appointments (0, 16 and 52 weeks). Spirometry was performed to record FEV1 (forced expiratory volume in one second) and FVC (forced vital capacity) according to ATS/ERS criteria using a hand-held spirometer. [255] Study participants were not required to stop using their inhalers prior to spirometry testing.[2] Reversibility testing was not required at any visit.

All spirometers passed validation checks using a three-litre syringe prior to use with a participant on a day of testing. At Visit 1, a full blood count was taken to measure eosinophil count. This was recorded to two decimal places to increase the granularity of this result.

3.12.5 Visits 2 to 6

At each subsequent visit, ACQ-5 was performed. Participants were also asked about any asthma exacerbations and GP, ED or hospital attendances since the preceding visit. Data on the start and end date of any asthma exacerbation, date of healthcare contact, dose and duration of prednisone were recorded.

The worksheet prompt questions were:

- Since the last study visit, have you been admitted to hospital because of your asthma?

- Have you attended the ED because of your asthma, but not been admitted to hospital?
- Have you been to the after-hours GP because of your asthma?
- Have you made an unplanned visit to your GP because of your asthma?
- Since the last study visit have you taken a course of steroids for your asthma?

A photocopy of the asthma action plan on which the participant had recorded the data was taken, and cross-checks with hospital records and GP databases were performed to confirm dates and doses.

Inhaler technique was assessed and asthma action plans were reviewed at each visit. Previously dispensed inhalers were reviewed and replacements issued as required. At Visit 3 and 6, FE_{NO} and spirometry were performed. At Visit 6 all previously dispensed study inhalers were collected and an interim prescription provided to the participant prior to review with their own GP. A letter was sent to each participant's GP informing them of the participant's completion of the study.

3.12.6 Unscheduled visits

Participants were asked to contact the investigator between appointments if their healthcare provider made any change to their randomised treatment, if they were concerned they would run out of inhaler medication or that their study inhalers were not working correctly, if they wished to withdraw from the study or if they became pregnant. In each case an unscheduled visit was booked.

If a study participant had an exacerbation during the study, they were asked to contact their GP for assessment and management, or visit ED/after-hours clinic in accordance with their action plan. It was reinforced to the study participants that they would 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 were advised that should they need to take more than eight 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 were advised that should they need to 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 their action plan, if participants usually measured their own peak flow at home, they continued to do this and were asked to seek medical review if their peak flow dropped to below 60% of their best measurement.

The comparative efficacy of the medication regimens on asthma control was the primary 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 were reported as adverse events (AEs) or serious adverse events (SAEs), if applicable and were also reported on the severe asthma exacerbation log within the eCRF. If a participant reported a worsening of asthma that did not meet the criteria for an exacerbation (e.g. feeling more wheezy than usual, worse ACQ score), this was considered part of the fluctuating course of asthma, and not to be an AE.

If a participant self-reported high use (>16 puffs of Terbutaline or >eight puffs of budesonide/formoterol in a 24 hour period) without medical review in the past seven days, they were advised to seek medical review from their GP or usual healthcare provider in accordance with their action plan. If it was apparent that there might be difficulty in obtaining such a medical review in a timely manner, then they were given a five-day prescription for prednisone (in accordance with their action plan), and advised to seek further medical review if their symptoms did not improve. If the investigator considered that the participant required urgent medical assessment and treatment, then the investigator referred the participant to the appropriate after hours/ED service.

3.12.7 Study inhalers

At the first appointment, each participant was educated in how to correctly use the study Turbuhaler with a demonstration and written instructions. At each subsequent appointment, inhaler technique was assessed according to the checklist below and education provided if inhaler technique was not satisfactory.

Essential steps of good Turbuhaler technique were:

- Unscrew and remove cover
- Keep inhaler upright while twisting grip
- Twist around and back until click is heard
- Breathe in strongly and deeply

Participants were advised not to share inhalers and not to use other non-study inhalers or nebulisers unless indicated by their doctor. If they did use non-study inhalers or nebulisers they were asked to contact the study co-ordinator who documented the date, time and dose. Participants were neither encouraged nor discouraged from using their reliever inhaler before exercise to prevent

exercise induced asthma. They were 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.

3.12.8 Asthma management plans

Participants were issued with an asthma action plan relevant to their randomised group (see Appendix). This plan is a modified version of the "Symbicort SMART Asthma Action Plan" promoted by the National Asthma Council of Australia. [256] The purpose of providing these plans was to reinforce the randomised treatment regimens and provide written instructions on what actions the participant should take in the situation of worsening asthma, in particular when to seek GP review and emergency medical care. Based on international adult asthma guidelines, including those of New Zealand, more than 16 actuations of terbutaline and eight actuations of budesonide/formoterol per 24 hours was considered the threshold that required medical review. A cut off of more than 24 actuations per day of terbutaline and 12 actuations per day of budesonide/formoterol was described as the threshold requiring same day GP or hospital review. [247,257–259] Previous studies assessing the safety of as-needed formoterol have described a maximum threshold of 12 actuations per day. [146,258,260,261]

On the back of each asthma action plan was a space to record 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).

The use of an asthma self-management plan with regular review is associated with improved health outcomes through improved adherence to therapy, recognition of deteriorating symptoms and earlier treatment with systemic corticosteroids for severe asthma exacerbations [262]. It was for this reason that the provision of written asthma self-management plans, with access to peak flow versions if a patient was familiar with this as part of their pre-study self-management strategy, was an important feature of this real-world study. It was recognised that issuing each participant with an asthma management plan may improve asthma control and reduce the number of exacerbations. Given that issuing all asthmatics with a personalised asthma management plan is a tenet of all asthma guidelines, it was felt that this was a mandatory part of standard care within the study protocol. As all participants received an action plan this would have affected both groups equally.

Participants were reminded of the details of the asthma action plan at each visit and were asked to bring all dispensed inhalers to each visit. The number of inhalers dispensed depended on the randomised treatment, the time to the next visit and inhaler use over the previous treatment period. Inhaler medication returned at the study visits was stored until the sponsor (MRINZ) confirmed it

could be destroyed. Participants were not required to measure their peak flow or to fill in a record card every day as this is generally poorly performed leading to missing data and participants documenting what the physician wants to see. [263–266] Additionally, record cards would have prompted the participants to take their medications more regularly and promote adherence, reducing the chance of seeing any difference between the regular and reliever ICS regimens which might occur in a real-world scenario.

3.12.9 Withdrawal from study

Participants could decide to withdraw from the study and withdraw consent at any stage. Equally, participants were withdrawn by the investigator if there was concern about their safety at any point during the study. In each case, follow-up arrangements with the participant's GP were made. Additional reasons for study withdrawal included if the participant was found to have been incorrectly enrolled in the study, became pregnant, or if their prescribed randomised treatment was increased by their GP or other healthcare provider for more than 14 days. Randomised treatment modifications were defined as an increase in the participant's randomised asthma inhaler regimen and 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. If a modification resulted in a decrease in the participant's randomised asthma inhaler regimen this was not a cause for withdrawal. Participants who did have a reduction were encouraged by the investigator to return to their randomised regimen.

Females who were pregnant, breastfeeding or planning pregnancy at the time of recruitment were excluded from participating in the trial, and enrolled participants who became pregnant during the course of the trial were withdrawn from the study. Current clinical practice allows for the use of budesonide or budesonide/formoterol during pregnancy, as the benefits to both mother and child of adequate asthma control outweigh the theoretical risks of treatment. Pregnancy can affect asthma control, however, and continued enrolment may therefore have influenced the study outcome. Furthermore, it is preferable for the mother to be on a tailored asthma management regimen rather than a randomly allocated trial regimen. Enrolled participants who became pregnant were asked to contact the researchers after the birth of the baby. Any congenital anomaly or birth defect were considered to be a serious adverse event.

An unscheduled withdrawal visit (performed as a Visit 6) was performed once an investigator was aware of the need for withdrawal. Participants were asked to return all their study inhalers at this visit and an interim prescription for asthma medication was provided pending review with their usual medical provider.

3.13 Adverse events

An adverse event is any untoward medical occurrence in a study participant temporally associated with participation in the trial and the administration of study medication, whether or not this was considered related to the medicine. A worsening of a pre-existing medical condition other than asthma was considered an adverse event.

At each follow-up visit, the investigator specifically enquired as to whether the participant had had any medical review, if any systemic corticosteroids or any other medication had been used for asthma other than the randomised study regimen, and whether there had been any other changes to medication. Hospital attendances were verified using documentation from the participant, GP or hospital database.

Participants were asked to grade adverse events and the maximum severity was 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)

An assessment of causality and expectedness was performed by the investigator submitting the adverse event report. Causality was based on the investigator's judgement of whether the event was related, or not related, to the study inhalers. Expectedness was assessed against the Medsafe Data sheet for each study drug.

For the purposes of this study the following events were considered to be serious adverse events and required reporting within 24 hours of the investigator becoming aware of the event through entry into the eCRF.

- 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

All serious adverse events were reviewed monthly by a data safety monitoring (DSMC) committee.

3.14 Sample size calculation

The primary outcome variable of the study was the rate of severe asthma exacerbations per patient per year. Assuming a drop-out rate of 10%, 890 patients were 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 baseline rate of severe exacerbations per patient per year of 0.30 was derived from randomised controlled trials 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 [69] and rates in subjects previously treated with ICS at baseline of 0.92 and 0.96 (budesonide 200 and 400μg/day),[69] 0.35 (budesonide 800μg/day),[70] and 0.35 (budesonide 400μg/day). [267] 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,[71,211] and a non-significant 38% reduction in severe exacerbations with ICS and SABA reliever therapy (separate inhalers) vs physician-adjusted maintenance ICS.[234] This 38% reduction in severe exacerbations was expected to be less than that observed in this 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 were directly relevant to the PRACTICAL study and for the purpose of the power calculation, a conservative relative rate of severe exacerbations per patient per year of 0.62 with the ICS/LABA reliever regimen was estimated.

3.15 Statistical analysis

I am grateful to Professor Mark Weatherall for advising on the design of the statistical analysis plan and undertaking the analysis.

3.15.1 Baseline data description

Continuous variables were summarised by mean and standard deviation (SD); median and inter-quartile range (IQR); minimum (Min) to maximum (Max). Categorical and ordinal variables were summarised by counts and proportions expressed as a percentage.

3.15.2 Primary outcome variable analysis

This was 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 was by Poisson regression with an offset for the time of observation. Over-dispersion was evaluated prior to analysis and a corrected analysis applied.
A sensitivity analysis included 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 FE_{NO} and baseline blood eosinophil count. This accounted for different distributions of these variables in the treatment groups and increased precision of the estimates of differences.

3.15.3 Secondary outcome variable analyses

Survival analysis was 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 and time to first exacerbation.

Simple t-tests by time of measurement and mixed linear models for repeated measures by time were used for ACQ-5, FEV1, FEV1 percentage predicted and FE_{NO} on a logarithm transformed scale. Comparison of proportions by logistic regression were used to analyse the proportion of severe exacerbations defined by each criterion, the proportion of participants with at least one severe exacerbation, the proportion of participants withdrawn and reason, adverse events and serious adverse events.

3.15.4 Subgroup Analyses

Sub-group analyses were performed for two outcome variables: rate of severe exacerbations and ACQ-5. In these sub-group analyses the differential effect of treatment on outcome were 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
- Baseline ACQ-5 score (for severe exacerbation outcome only)
- Baseline FEV1 % predicted
- Baseline FE_{NO}
- Baseline blood eosinophil count

A sensitivity analysis for potential confounding variables used Poisson regression with an offset for time in the study to estimate the relative rate of severe exacerbation in relation to potential confounding variables. This used each potential confounding variable on its own (univariate associations) and then all potential confounding variables in the same model (multivariate analysis).

A sensitivity analysis for potential effect modifying variables used Poisson regression with an offset for time in the study for the relative rate of severe exacerbation with each variable, in a model which included its main effect and interaction with treatment. For continuous variables except the ACQ-5, the 25th and 75th percentile values were used to illustrate the potential effect modification. For the ACQ-5 the effect of a 0.5 unit change was used based on the minimally clinically important difference (MCID).

3.16 Safety and Data Safety Monitoring committee

A DSMC reviewed all serious adverse events, protocol deviations and withdrawals for pooled data on a monthly basis. They also reviewed the results of the blinded interim statistical analysis to assess all unplanned hospital admissions for asthma, masked to treatment allocation, at the point when 500 participants had been randomised. The calculated interim p value for performing a safety review of the study was 0.006 (using a one-sided O'Brien-Fleming boundary). The proportion of participants with an unplanned hospitalisation for asthma was compared to the expected proportion of 2.0% using the binomial test for proportions. The observed rate did not exceed the expected rate with a p value <0.006, therefore a safety review of the study was not undertaken.

3.17 Monitoring

Given the size of the study, several study monitors monitored the study in accordance with GCP guidelines to assess site performance, to confirm recruitment rates, to ensure protocol adherence and to review study drug accountability. Monitors performed source data verification e.g. verifying the severe exacerbation data entered into eCRF against the source data for each subject. Remote monitoring of data also took place to ensure any logical inconsistencies or missing data were resolved prior to the on-site monitoring visit, and throughout the study.

The eCRF provided inbuilt validation checks to ensure consistent and correct data were entered. A close-out visit was performed once the study had completed, to formally close out each site and to ensure any ongoing responsibilities, for example, following up adverse events, were met.

3.18 Ethics

All patients were randomised to receive ICS. Participants deemed to be at 'high risk' were excluded. High risk patients were identified on the basis of a previous ICU admission or if they had uncontrolled asthma despite satisfactory inhaler technique and ≥80% adherence to their prescribed ICS treatment prior to recruitment. Participants were followed closely during the study with provision of asthma action plans. Investigators at each site could choose to withdraw a study participant at any time due to safety concerns, including if they had concerns that a participant had uncontrolled asthma requiring a step up in therapy.

The study did not require a 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. The study is not therefore under the scope of Medsafe review or the need for approval under Section 30 of the Medicines Act 1981.

Ethical Submission was made to the Northern B Deanery Health and Disability Ethics Committees of New Zealand (HDEC). Locality approval was granted at each site before any participants were recruited, as per ethics committee guidelines.

I asked the ethics committee for approval of all the advertising used to recruit patients for the study. I submitted all substantial changes made to the participant information sheet and consent form for ethics committee review.

The participants' anonymity was maintained throughout the study. No study reports contained any information that could individually identify a study participant. The participants were identified by a randomisation ID number on study documents that were sent outside of the individual study site. The eCRF captured participant initials, date of birth and ethnicity, as part of demographic information. All documents were stored securely and only accessible by study staff. Participants were reimbursed for travel costs, according to local practice and in accordance with ethical approval.

I registered the trial with the Australian New Zealand Clinical Trials Registry; ACTRN 12616000377437.

The study was funded by the Health Research Council of New Zealand who did not have any involvement in the study design, data collection, analysis or interpretation.

3.19 Protocol updates after study commencement

Protocol version 2.0 was the current version at the time the trial began in May 2016.

Date of update	Rationale
Version 2.0 (31 March 2016) to Version 2.1 (08 May 2016)	• Updated so that asthma management plans reflect those issued to participants
Version 2.1 (08 May 2016) to Version 3.0 (04 Oct 2016)	• Statement to reflect fact that a blinded re-estimation of the sample size performed by the study statistician was planned to be performed at the interim analysis point to ensure that the study could meet the primary outcome with regard to exacerbation event rate • Statement added that if at the point of blinded sample size re-estimation a considerable increase in recruitment was required and this was not achievable, a blinded sample size re-estimation using the outcome of asthma exacerbations per patient per year rather than severe asthma exacerbations per patient per year would be performed • Time to first exacerbation added as a secondary outcome variable
Version 3.0 (04 Oct 2016) to Version 4.0 (21 Feb 2018)	• Update to investigator list • Clarification that periostin only collected in a sub-group recruited at MRINZ • Update to wording to reflect fact that rather than collecting and keeping participants pre-study inhalers, the participant was asked to secure them somewhere safely at home/dispose of them • Update to wording to reflect fact that number of inhalers issued depended on Turbuhaler use in the previous treatment period and time to next visit

• Table 5: Summary of updates made to protocol over course of trial

4. CHAPTER FOUR: RESULTS

4.1 Trial Timelines

A total of 890 participants were enrolled between 5 May 2016 and 22 December 2017. The recruitment of participants by site is shown in Table 6.

Date	Milestone
18 November 2015	Ethics approval and RAG-M review
23 March 2016	Clinical trial registration on ANZCTR (ACTRN12616000377437)
April 2016	MRINZ given site approval
5 May 2016	Recruitment commences at MRINZ
20 May 2016	South Pacific given site approval
31 May 2016	Greenhithe given site approval
4 July 2016	Henderson given site approval
26 July 2016	Southern given site approval
11 August 2016	Lakeland Clinical Trials given site approval
19 October 2016	Coastal Medical Rooms given site approval
31 October 2016	Clinical Horizons given site approval
November 2016	25% recruited
24 February 2017	Lower Hutt After Hours given site approval
24 February 2017	Optimal Clinical Trials given site approval
7 March 2017	Waikanae Medical Centre given site approval
13 April 2017	RMC research given site approval
22 June 2017	Team Medical given site approval
18 May 2017	Papamoa Pines given site approval
5 October 2017	P3 Research given site approval
April 2017	50% recruited
17 May 2017	Interim safety statistical analysis performed
September 2017	75% recruited
November 2017	Papakura Marae given site approval
22 December 2017	100% recruited
December 2018	Final participant completed study
February 2019	Database cleaning complete and analysis commenced

• Table 6: Study timeline

4.2 Recruitment of participants by site

Site	Number of participants recruited
Medical Research Institute	321
Henderson	73
Southern Clinical Trials	23
South Pacific	46
Greenhithe	39
Waikanae Medical Centre	2
Papamoa Pines	24
Lakeland	14
Clinical Horizons	34
Team Medical	5
Coastal Medical Rooms	14
RMC Research	38
Lower Hutt after hours	128
Optimal Clinical Trials	112
P3 Medical Research	17
Papakura Marae	0

• Table 7: Recruitment of participants by site

I ran the Medical Research Institute and Lower Hutt after-hours clinics alongside other Institute staff.

4.3 Interim safety analysis

At the point of the interim analysis, there had been no admissions to hospital due to asthma in either arm of the study. This was the protocol-specified criteria for safety review and given there were no reported events, the data safety monitoring committee did not recommend a safety review of the study.

4.4 Sample size re-estimation at the blinded interim analysis point

A blinded re-estimation of the required sample size for the trial, masked as to treatment allocation and based on the rate of severe exacerbations in each of the arms of the study, was performed at the interim analysis point when 500 participants had been recruited to the study. At the onset of the study, the sample size of 890 participants was based on an assumed rate in the ICS and 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 as-needed budesonide/formoterol arm, a relative rate of 0.62.

It was decided prior to the interim analysis that if, in the blinded assessment of rate of severe exacerbations in the two treatment arms, the higher of these two event rates was less than 0.30 events per year, then the sample size requirements would be larger than currently planned and a decision would be taken as to whether this increase could be reasonably achievable or not. If not achievable, a blinded sample size estimation using an outcome of 'asthma exacerbations per patient per year' would be performed and consideration taken as to whether the primary outcome variable should be changed from severe asthma exacerbations per patient per year to asthma exacerbations per patient per year.

At the interim analysis, the 500 enrolled participants had been in the study for a mean of 0.46 years (SD 0.30) with a total of 230 participants-years observation (500*0.46). The study had been recruiting for just under 12 months at the point of the interim analysis. 27% of the study had been completed in terms of participant/years. Estimates of exacerbation rates were made on relatively small numbers. There had been a total of 20 severe exacerbations, 20/230=0.09 (95% CI 0.07 to 0.11) rate of severe exacerbations per participant year of observation. There had been 31 exacerbations 31/230 = 0.13 (95% CI 0.11 to 0.17) rate of total exacerbations per participant year of observation. The rate of severe exacerbations at the point of the interim analysis of 0.09 was lower than the 0.30 originally anticipated. This meant that the required sample size for the study to be adequately powered to see a significant difference in severe exacerbations between the two groups would be of the order of 2112 participants (950 per arm). Changing the primary outcome variable to include exacerbations would require 1512 participants (680 per arm). Neither the

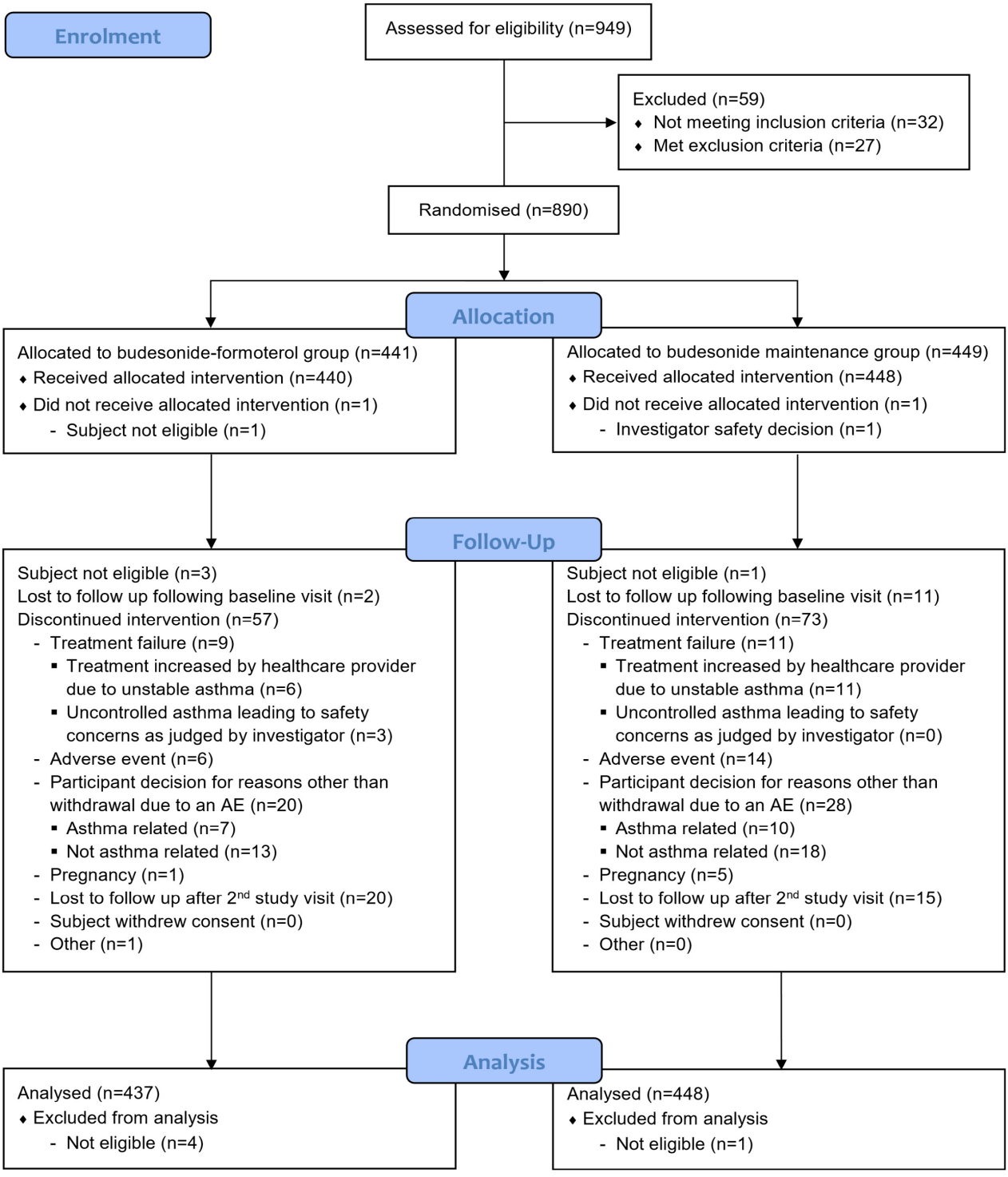
funding nor the capacity was in place to allow this, and therefore the study continued with the original primary outcome variable and planned sample size of 890 with no change in recruitment practices, although it was accepted that this may result in the study being underpowered to demonstrate a significant difference in rate of severe exacerbations between the treatment groups.

The table below demonstrates the simulation based estimates to detect a relative rate of 0.62 (the original study design was to detect a rate of 0.30 going to a control rate of 0.185 for a relative rate of 0.62) with 80% power (original study design was for 90% power) and type 1 error rate 5%.

Control rate	Treatment rate (0.62 relative rate)	N per arm not accounting for drop-out	Total with two arm trial and 10% drop-out
Point estimate & upper confidence limit from severe exacerbation definition 80% power			
0.09	0.056	950	2112
0.11	0.068	800	1778
Point estimate & upper confidence limit from total exacerbation definition 80% power			
0.13	0.081	680	1512
0.17	0.11	620	1378
Original sample size calculation (90% power)			
0.30	0.185	400	890

- Table 8: Simulated exacerbation rate and effect on required sample size

4.5 CONSORT Flow Diagram



• Figure 13: CONSORT flow diagram

A total of 890 participants were enrolled to the study between 5th May 2016 and 22nd Dec 2017 with the last participant completing the study on 22nd December 2018. 94% of the participants screened were eligible for the study. The most common reason for ineligibility was pack year smoking history. No follow-up data were available in 14 participants (two in the budesonide/formoterol arm, 12 in budesonide maintenance arm). Five participants were randomised in error and ineligible; as a result the intention to treat dataset included 885 participants, 437 in the budesonide/formoterol arm and 448 participants in the budesonide maintenance arm.

4.6 Characteristics of trial participants

The characteristics of participants are shown below. The groups were well balanced. A total of 55% of participants were female and 7% were current smokers. Lung function was preserved (mean FEV1 84% +/- 21.4% predicted). Most participants (70.2%) were taking an inhaled glucocorticoid at baseline making the study representative of those with mild-moderate asthma. A total of 28% of all participants reported uncontrolled asthma, and 12% of participants reported a severe exacerbation in the previous 12 months. Mean ACQ-5 score was 1.15.

Characteristics	Budesonide/formoterol group (n=437)	Budesonide maintenance group (n=448)
Age – yr	43.3±15.2	42.8±16.7
Age at diagnosis – yr	19.5±17.7	18.8±18.1
Body Mass Index	29.4±7.1	28.0±5.8
Female sex – no. (%)	244 (55.8)	241 (53.8)
Ethnicity		
Asian	29 (6.6)	34 (7.6)
European	342 (78.3)	357 (79.7)
Maori	41 (9.8)	31 (6.9)
Other	5 (1.1)	10 (2.2)
Pacific	20 (4.6)	16 (3.6)
Smoking Status – no. (%)		
Current smokers	39 (8.9)	24 (5.4)
Ex-smokers	123 (28.2)	112 (25.0)
Never smokers	275 (62.9)	312 (69.6)
Pack years (among ever smokers)	4.5±4.7	4.6±4.7

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Characteristics	Budesonide/formoterol group (n=437)	Budesonide maintenance group (n=448)
Participant-reported ICS use in the 12 weeks prior to enrolment – no. (%)	305 (69.8)	316 (70.5)
Self-reported ICS adherence in 4 weeks prior to enrolment – (%)[¥]	54.8 ±37.0 N=304	58.6 ±47.3 N=315
Participant-reported ICS use ever - no. (%)	390 (89.2)	381 (85.0)
Participant-reported SABA use in four weeks prior to enrolment - no. of occasions per week		
Mean	4.3±6	4.9±7.5
Median (IQR)	2 (1-5.5)	2.3 (1-6)
Min to max	0-70	0-84
No. of hospital admissions for asthma (lifetime) — mean per participant	0.7 ±5.1	0.5 ±2.1
Severe exacerbation in the previous 12 months – no. (%)		
0	384 (87.9)	396 (88.4)
1	45 (10.3)	41 (9.2)
2	5 (1.1)	7 (1.6)
3	3 (0.7)	3 (0.7)
4	0 (0)	1 (0.2)
Any	53 (12.1)	52 (11.6)
ACQ-5 score†	1.1±0.8	1.2±0.8
GINA symptom control – no. (%)		
Well-controlled	101 (23.1)	103 (23.0)
Partly controlled	209 (47.8)	226 (50.5)
Uncontrolled	127 (29.1)	119 (26.6)
On-treatment FEV_1 - % of predicted value[‡]	87.8±16.4	87.4±16.3
Median FeNO (IQR) – ppb	26 (15 to 51)	30 (18 to 62.5)
Blood eosinophil count – $x10^{-9}$ per litre	0.3±0.2	0.3±0.2

• Table 9: Characteristics of trial participants

4.7 **Primary Outcome - Annualised Severe Exacerbation Rate**

A severe exacerbation was defined in the study as i) at least three days of systemic glucocorticoids or ii) hospital/emergency department systemic glucocorticoid treatment for asthma.

The severe asthma exacerbation rate was lower with budesonide/formoterol than budesonide maintenance (absolute rate per patient per year, 0.119 vs 0.172; relative rate, 0.69; 95% CI, 0.48-1.0; p=0.049).

Comparison	Relative rate (95% CI)	P
Budesonide/formoterol group vs. budesonide maintenance group	0.69 (0.48 to 1.0)	0.049

- Table 10: Poisson regression-derived estimates of relative rate of severe exacerbations between treatment groups

Treatment	Relative rate (95% CI)
Budesonide/formoterol group	0.119 (0.089 to 0.157)
Budesonide maintenance group	0.172 (0.136 to 0.218)

- Table 11: Poisson regression-derived estimates of rates of severe exacerbations by treatment group

The proportion of participants with no observed time of observation were: Budesonide/formoterol as needed, 2/437 (0.5%) and budesonide maintenance and terbutaline reliever, 12/448 (2.7%).

Budesonide/formoterol: 48 severe exacerbations in 405.0 participant-years of observation, 0.12 exacerbations per participant-year observation.

Budesonide maintenance: 68 severe exacerbations in 396.1 participant-years of observation, 0.17 exacerbations per participant-year observation.

Budesonide/formoterol N=437				
Variable	Mean (SD)	Median (IQR)	Min to Max	Sum
Severe exacerbation no.	0.11 (0.40)	0 (0 to 0)	0 to 4	48
Time in study (days)	338.3 (81.5)	364 (362 to 366)	0 to 447	147838
Time in study (years)	0.93 (0.22)	1.0 (0.99 to 1.0)	0 to 1.2	405.0
Budesonide N=448				
Variable	Mean (SD)	Median (IQR)	Min to Max	Sum
Severe exacerbation no.	0.15 (0.42)	0 (0 to 0)	0 to 3	68
Time in study (days)	322.7 (100.6)	364 (361 to 366)	0 to 476	144565
Time in study (years)	0.88 (0.28)	1.0 (0.99 to 1.0)	0 to 1.3	396.1

- Table 12: Severe exacerbation number and time of observation in study by treatment arm

At least one severe exacerbation was reported in 37/437 (8.5%) participants in the budesonide/formoterol group and 59/448 (13.2%) participants in the budesonide maintenance group. The relative risk of at least one severe exacerbation with budesonide/formoterol versus budesonide maintenance was 0.80 (95% CI, 0.67 to 0.95).

	Treatment N/N (%)	
No. of severe exacerbations experienced by participants during follow-up	Budesonide/formoterol group N=437	Budesonide maintenance group N=448
0	400 (91.5)	389 (86.8)
1	28 (6.4)	51 (11.4)
2	8 (1.8)	7 (1.6)
3	0 (0)	1 (0.2)
4	1 (0.2)	0 (0)
Total severe exacerbations	48	68
Crude rate of severe exacerbations per participant year of follow-up	0.12	0.17

- Table 13: Number of severe exacerbations experienced by participants during follow-up by treatment group

Five severe exacerbations in the budesonide/formoterol group and 9 severe exacerbations in the budesonide maintenance group were defined by the need for an ED visit or hospitalisation.

	Treatment N/N (%)	
ED visit/Hospitalisation count	Budesonide/formoterol group N=37	Budesonide maintenance group N=59
0	33 (89.2)	51 (86.4)
1	3 (8.1)	7 (11.9)
2	1 (2.7)	1 (1.7)
Total ED visit/hospitalisations	5	9
Systemic corticosteroids prescribed for at least 3 days		
0	0 (0)	0 (0)
1	28 (75.7)	51 (86.4)
2	8 (21.6)	7 (11.9)
3	0 (0)	1 (1.7)
4	1 (2.7)	0 (0)
Total corticosteroid courses	48	68

- Table 14: Types of severe exacerbation by treatment arm when a participant had at least one severe exacerbation during follow-up

4.8 Annualised exacerbation rate

Exacerbation rate was defined in the study as worsening asthma resulting in unplanned medical review (primary care, ED, hospital admission) and/or worsening asthma resulting in use of systemic glucocorticoids for any duration.

The asthma exacerbation rate was lower with budesonide/formoterol than budesonide maintenance (absolute rate per patient per year, 0.165 vs 0.237; relative rate 0.70; 95% CI, 0.51-0.95).

Comparison	Relative rate (95% CI)
Budesonide/formoterol group vs. budesonide maintenance group	0.70 (0.51 to 0.95)

- Table 15: Poisson regression-derived estimate of the relative rate of exacerbations between treatment groups

Treatment	Relative rate (95% CI)
Budesonide/formoterol group	0.165 (0.130 to 0.210)
Budesonide maintenance group	0.237 (0.194 to 0.291)

- Table 16: Poisson regression-derived estimates of rates of exacerbations by treatment group

Budesonide/formoterol: 67 exacerbations in 405.0 participant-years of observation, 0.16 exacerbations per participant-year observation.

Budesonide maintenance: 94 exacerbations in 396.1 participant-years of observation, 0.24 exacerbations per participant-year observation.

Budesonide/formoterol N=437				
Variable	Mean (SD)	Median (IQR)	Min to Max	Sum
Exacerbation no.	0.15 (0.49)	0 (0 to 0)	0 to 4	67
Time in study (days)	338.3 (81.5)	364 (362 to 366)	0 to 447	147838
Time in study (years)	0.93 (0.22)	1.0 (0.99 to 1.0)	0 to 1.2	405.0
Budesonide N=448				
Variable	Mean (SD)	Median (IQR)	Min to Max	Sum
Exacerbation no.	0.21 (0.49)	0 (0 to 0)	0 to 3	94
Time in study (days)	322.7 (100.6)	364 (361 to 366)	0 to 476	144565
Time in study (years)	0.88 (0.28)	1.0 (0.99 to 1.0)	0 to 1.3	396.1

- Table 17: Exacerbation number and time of observation in study by treatment arm

At least one exacerbation was reported by 49/437 (11.2%) participants in the budesonide/formoterol group and 79/448 (17.6%) in the budesonide group. The relative risk of at least one exacerbation in the budesonide/formoterol group versus the budesonide maintenance group was 0.79 (95% CI 0.68 to 0.92).

	Treatment N/N (%)	
No. of exacerbations experienced by participants during follow-up	Budesonide/formoterol group N=437	Budesonide maintenance group N=448
0	388 (88.8)	369 (82.4)
1	36 (8.2)	65 (14.5)
2	9 (2.1)	13 (2.9)
3	3 (0.7)	1 (0.2)
4	1 (0.2)	0 (0)
Total exacerbations	67	94
Crude rate of per participant year of follow-up	0.16	0.24

- Table 18: Number of exacerbations and severe exacerbations experienced by participants during follow-up by treatment group

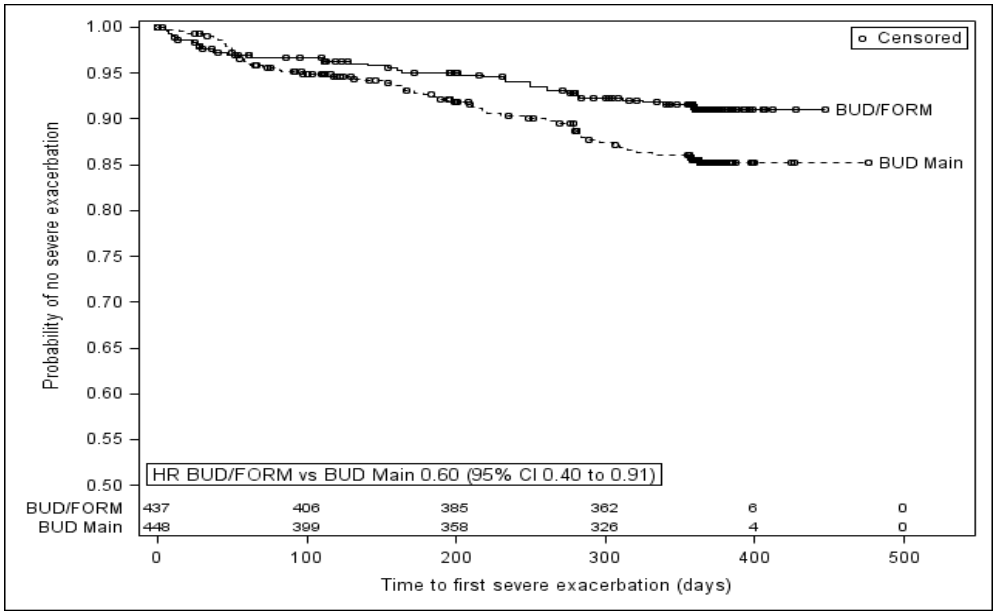
A total of 15 exacerbations in the budesonide/formoterol group and 25 exacerbations in the budesonide maintenance group were defined by the need for medical review but did not require a course of glucocorticoids.

	Treatment N/N (%)	
No. of medical reviews experienced by participants during follow-up	Budesonide/formoterol group N=49	Budesonide maintenance group N=79
0	0 (0)	0 (0)
1	36 (73.5)	65 (82.3)
2	9 (18.4)	13 (16.5)
3	3 (6.1)	1 (1.3)
4	1 (2.0)	0 (0)
Total medical reviews	67	94
No. of courses of systemic glucocorticoids taken by participants during follow-up		
0	9 (18.4)	19 (24.1)
1	30 (61.2)	52 (65.8)
2	9 (18.4)	7 (8.9)
3	0 (0)	1 (1.3)
4	1 (2.0)	0 (0)
Total corticosteroid courses	52	69

- Table 19: Types of exacerbation by treatment group when a participant had at least one exacerbation during follow-up

4.9 Time to first severe exacerbation

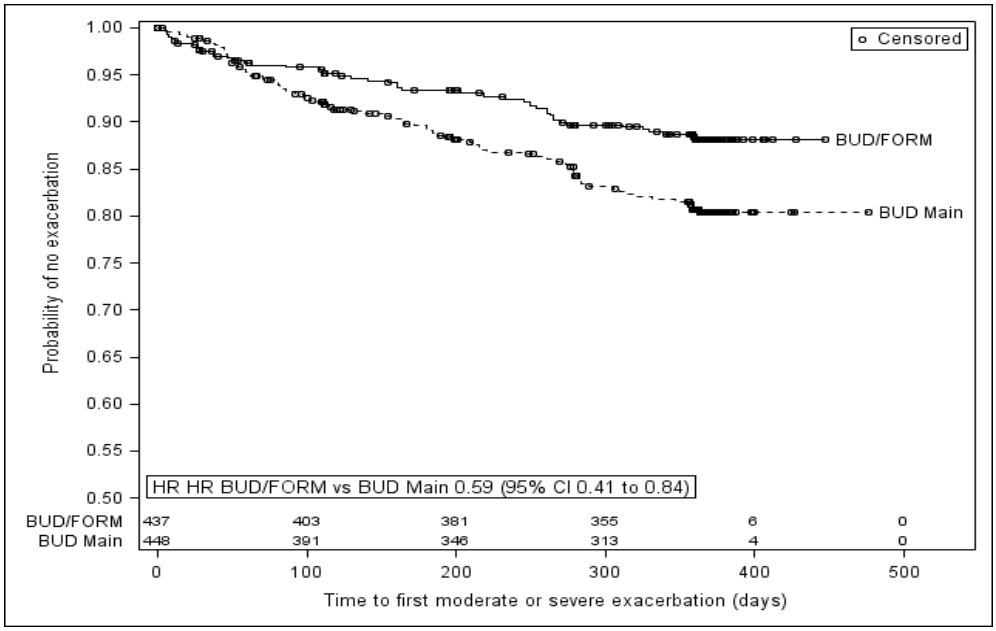
Time to first severe exacerbation was longer with budesonide/formoterol than budesonide maintenance (hazard ratio, 0.60; 95% CI, 0.40-0.91, p = 0.015).



- Figure 14: Kaplan–Meier estimates of the first occurrence of severe exacerbation in a time-to-event analysis

4.10 Time to first exacerbation

Time to first exacerbation was longer with budesonide/formoterol than budesonide maintenance (hazard ratio 0.59; 95% CI, 0.41-0.84).



- Figure 15: Kaplan–Meier estimates of the first occurrence of exacerbation in a time-to-event analysis

4.11 Asthma Control Questionnaire (ACQ)

Participants had a mean ACQ-score of 1.15. Across all time points, the ACQ-5 score with budesonide/formoterol was not different from budesonide maintenance (mean difference, 0.06; 95% CI, -0.005-0.12).

Visit	Budesonide/formoterol group mean (SD)	Budesonide maintenance group mean (SD)
Baseline	1.13 (0.84) N=437	1.17 (0.84) N=448
2	0.97 (0.69) N=423	0.88 (0.70) N=427
3	0.87 (0.66) N=409	0.80 (0.73) N=399
4	0.84 (0.72) N=389	0.81 (0.82) N=377
5	0.83 (0.71) N=377	0.80 (0.85) N=367
6	0.86 (0.75) N=377	0.80 (0.85) N=367

• Table 20: ACQ data description by treatment

ACQ-5	Budesonide/formoterol group minus budesonide maintenance group
Visit	Estimate (95% CI)
2	0.10 (0.008 to 0.187)
3	0.07 (-0.021 to 0.161)
4	0.02 (-0.071 to 0.116)
5	0.02 (-0.072 to 0.117)
6	0.06 (-0.028 to 0.154)
Averaged over all visits‡	0.06 (-0.005 to 0.12)

• Table 21: Mixed linear model comparison of differences in ACQ-5 score with estimates of treatment difference by visit and baseline as a continuous co-variate between treatment groups

‡Interaction P = 0.58

4.12 Forced expiratory volume in one second (FEV_1)

Across all time points, the FEV_1 with budesonide/formoterol was not different from budesonide maintenance (mean difference, 0.006 liters; 95% CI, -0.026-0.04).

Visit	Budesonide/formoterol Mean (SD)	Maintenance budesonide Mean (SD)
Baseline	2.99 (0.90) N=436	3.02 (0.90)
3	3.04 (0.88) N=409	3.02 (0.88)
6	3.03 (0.88) N=401	3.03 (0.90) N=406

• Table 22: FEV1 data description by treatment arm

FEV1	Budesonide/formoterol minus maintenance budesonide	
Visit	Difference (95% CI)	P
3	0.014 (-0.021 to 0.05)	0.44
6	-0.001 (-0.036 to 0.03)	0.96
Averaged over all visits‡	0.006 (-0.026 to 0.04)	0.69

• Table 23: Mixed linear model comparisons with estimates of treatment difference by visit and baseline as a continuous co-variate

‡ Interaction p = 0.31

4.13 Fraction of Exhaled Nitric Oxide

The FE_{NO} was widely skewed at baseline; the median FE_{NO} was 26 parts per billion (ppb) (interquartile range [IQR], 15-51), with budesonide/formoterol and 30ppb (IQR, 18-62.5) with budesonide maintenance. At 12 months, the median FE_{NO} was 26ppb (IQR, 16-45) with budesonide/formoterol and 25ppb (IQR, 16-40) with budesonide maintenance. The geometric mean FE_{NO} across all time points with budesonide/formoterol was higher than with budesonide maintenance (ratio of geometric means 1.13; 95% CI, 1.07-1.21) equivalent to a median FE_{NO} difference of 5ppb. There was no evidence of treatment modification for FE_{NO} in relation to whether inhaled glucocorticoids were used at baseline or not, although those who used ICS at baseline had lower FE_{NO} levels throughout the study.

Visit	Budesonide/formoterol group median (IQR)	Maintenance budesonide group median (IQR)
Baseline	26 (15 to 51) N=437	30 (18 to 62.5) N=448
3	27 (16 to 46) N=409	25 (17 to 41) N=397
6	26 (16 to 45) N=401	25 (16 to 40) N=406

- Table 24: FE_{NO} data description by treatment group and visit number

Visit	Budesonide/formoterol group mean (SD)	Maintenance budesonide group mean (SD)
Baseline	3.33 (0.82) N=437	3.46 (0.90) N=448
3	3.33 (0.76) N=409	3.27 (0.69) N=397
6	3.29 (0.75) N=401	3.25 (0.73) N=406

- Table 25: log FE_{NO} data description by treatment and visit number

Visit	Budesonide/formoterol group minus budesonide maintenance group (difference 95% CI)	
3	0.13 (0.06 to 0.20)	P <0.001
Exponent	1.12 (1.07 to 1.22)	
6	0.12 (0.05 to 0.19)	P<0.001
Exponent	1.13 (1.05 to 1.21)	
Averaged over all visits‡	0.13 (0.07 to 0.19)	P<0.001
Exponent	1.13 (1.07 to 1.21)	

- Table 26: Mixed linear model comparison with estimates of treatment difference by visit

‡ Interaction p = 0.64 The exponent of the difference in logarithms is the ratio of geometric means.

Budesonide/formoterol group

Visit	No ICS at baseline	N	Median (IQR)
1		132	32.5 (15.0 to 61.5)
3		126	24.5 (18 to 49)
6		119	24 (16 to 41)
Visit	ICS at baseline	N	Median (IQR)
1		305	25 (15 to 48)
3		283	27 (16 to 46)
6		282	27 (17 to 46)

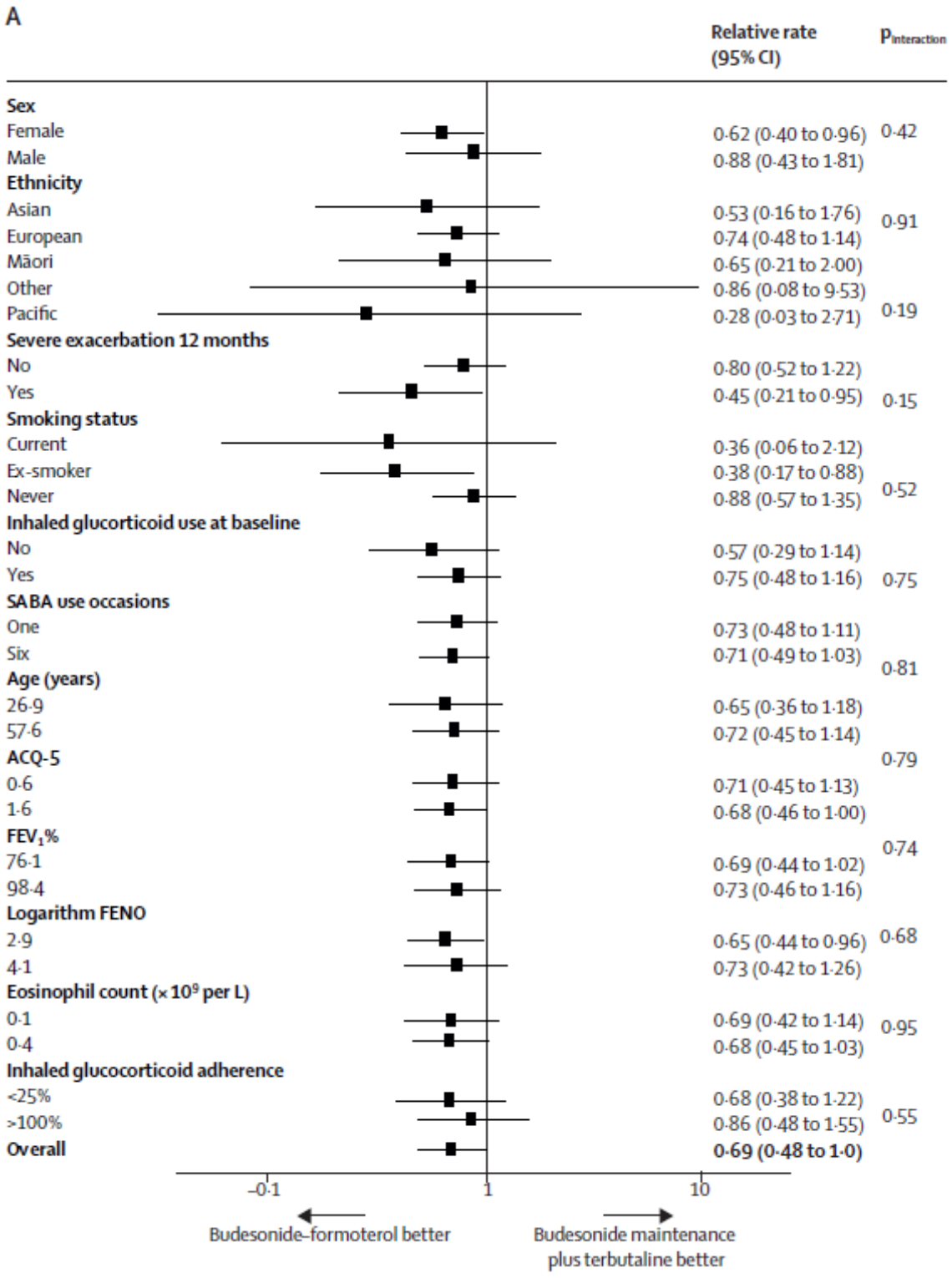
Budesonide maintenance group

Visit	No ICS at baseline	N	Median (IQR)
1		132	45.0 (23.0 to 91.0)
3		115	26 (17 to 45)
6		120	27 (16 to 43)
Visit	ICS at baseline	N	Median (IQR)
1		316	27.5 (16.5 to 54.0)
3		282	24 (16 to 39)
6		286	24 (15 to 39)

• Table 27: FE_{NO} data description by ICS use at baseline

4.14 Sensitivity analysis

In analyses testing the interaction of randomised treatment with various subgroups identified that the highest quartile of baseline blood eosinophils (>$0.4x10^9$/L) was associated with a greater reduction in ACQ-5, but not severe exacerbations, with budesonide maintenance compared with budesonide/formoterol. Otherwise there was no evidence of effect modification with respect to severe exacerbations or ACQ-5, based on baseline subgroups of age, sex, smoking status, exacerbation history, inhaled glucocorticoid use at baseline, adherence to inhaled glucocorticoid at baseline, baseline SABA use, ACQ-5, predicted FEV_1 and FE_{NO}.



- Figure 16: Differential effect of treatment on relative rate of severe exacerbation by potential effect modifying baseline variables

Inhaled glucocorticoid adherence was based on self-report over the previous four weeks. The relative rate is shown on the logarithm scale.

Budesonide/formoterol group versus budesonide maintenance group		
Comparison	P interaction	Relative rate of exacerbation (95% CI)
Overall	NA	0.69 (0.48 to 1.0)
Sex	0.42	
Female		0.62 (0.40 to 0.96)
Male		0.88 (0.43 to 1.81)
Ethnicity	0.91	
Asian		0.53 (0.16 to 1.76)
European		0.74 (0.48 to 1.14)
Maori		0.65 (0.21 to 2.00)
Other		0.86 (0.08 to 9.53)
Pacific		0.28 (0.03 to 2.71)
At least one severe exacerbation in the last 12 months	0.19	
No		0.80 (0.52 to 1.22)
Yes		0.45 (0.21 to 0.95)
Smoking status	0.15	
Current		0.36 (0.06 to 2.12)
Ex-smoker		0.38 (0.17 to 0.88)
Never smoker		0.88 (0.57 to 1.35)
Use of inhaled glucocorticoid at baseline	0.52	
No		0.57 (0.29 to 1.14)
Yes		0.75 (0.48 to 1.16)

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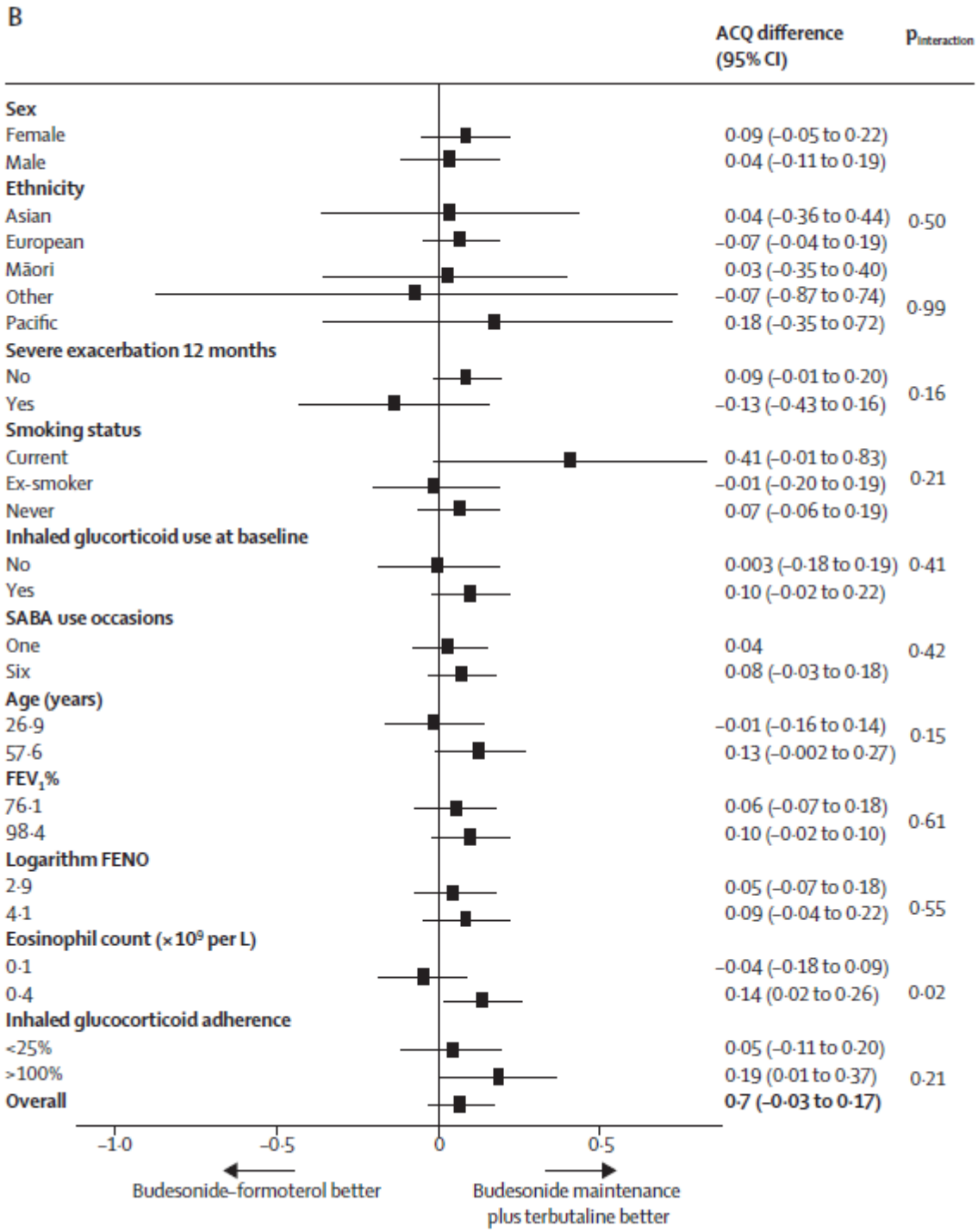
Budesonide/formoterol group versus budesonide maintenance group			
Comparison	Percentile of budesonide maintenance group	P interaction	Relative rate of exacerbation (95% CI)
Average no. of occasions of SABA use per week within the four weeks prior to randomisation		0.75	
1	25th		0.73 (0.48 to 1.11)
6	75th		0.71 (0.49 to 1.03)
Age		0.81	
26.9 years	25th		0.65 (0.36 to 1.18)
57.6 years	75th		0.72 (0.45 to 1.14)
ACQ-5		0.79	
0.6	25th		0.71 (0.45 to 1.13)
1.6	75th		0.68 (0.46 to 1.00)
FEV_1% predicted		0.74	
76.1	25th		0.69 (0.44 to 1.02)
98.4	75th		0.73 (0.46 to 1.16)
Logarithm FE_{NO}		0.68	
2.9	25th		0.65 (0.44 to 0.96)
4.1	75th		0.73 (0.42 to 1.26)
Eosinophil count $x10^{-9}$/L		0.95	
0.1	25th		0.69 (0.42 to 1.14)
0.4	75th		0.68 (0.45 to 1.03)
Percentage adherence to inhaled glucocorticoid in those using inhaled glucocorticoid at baseline N=609		0.55	
25	25th		0.68 (0.38 to 1.22)
100	75th		0.86 (0.48 to 1.55)

- Table 28: Treatment effect modification: interactions of baseline variables and the relative rate of severe exacerbations between treatment groups



• Figure 17: Differential effect of treatment on ACQ-5 by potential effect modifying baseline variables

Budesonide/formoterol group versus budesonide maintenance group		
Comparison	P interaction	ACQ-5 difference (95% CI)
Overall	NA	0.07 (-0.03 to 0.17)
Sex	0.50	
Female		0.09 (-0.05 to 0.22)
Male		0.04 (-0.11 to 0.19)
Ethnicity	0.99	
Asian		0.04 (-0.36 to 0.44)
European		0.07 (-0.04 to 0.19)
Maori		0.03 (-0.35 to 0.40)
Other		-0.07 (-0.87 to 0.74)
Pacific		0.18 (-0.35 to 0.72)
At least one severe exacerbation in the last 12 months	0.16	
No		0.09 (-0.01 to 0.20)
Yes		-0.13 (-0.43 to 0.16)
Smoking status	0.21	
Current		0.41 (-0.01 to 0.83)
Ex-smoker		-0.01 (-0.20 to 0.19)
Never smoker		0.07 (-0.06 to 0.19)
Use of inhaled glucocorticoid at baseline	0.41	
No		0.003 (-0.18 to 0.19)
Yes		0.10 (-0.02 to 0.22)

Table continued over page

Budesonide/formoterol group versus budesonide maintenance group			
Comparison	Percentile of budesonide maintenance group	P interaction	Relative rate of exacerbation (95% CI)
Average no. of occasions of SABA use per week, within the four weeks prior to randomisation		0.42	
1	25th		0.04 (-0.07 to 0.16)
6	75th		0.08 (-0.03 to 0.18)
Age		0.15	
26.9 years	25th		-0.01 (-0.16 to 0.14)
57.6 years	75th		0.13 (-0.002 to 0.27)
FEV_1% predicted		0.61	
76.1	25th		0.06 (-0.07 to 0.18)
98.4	75th		0.10 (-0.02 to 0.22)
Logarithm FE_{NO}		0.55	
2.9	25th		0.05 (-0.07 to 0.17)
4.1	75th		0.09 (-0.04 to 0.22)
Eosinophil count $x10^{-9}$/L		0.02	
0.1	25th		-0.04 (-0.18 to 0.09)
0.4	75th		0.14 (0.02 to 0.26)
Percentage adherence to inhaled glucocorticoid in those using inhaled glucocorticoid at baseline N=567		0.21	
25	25th		0.05 (-0.11 to 0.20)
100	75th		0.19 (0.01 to 0.37)

- Table 29: Treatment effect modification: interactions of baseline variables and the difference in ACQ-5 score between treatment groups

4.15 Treatment failure

The definition of treatment failure was:

a) Prescribed randomised treatment was increased by the participant's GP or other healthcare provider for >14 consecutive days during the study period, or
b) uncontrolled asthma resulting in safety concerns as judged by the investigator

The number of patients who were withdrawn due to treatment failure with budesonide/formoterol was not different from budesonide maintenance (9 vs 11; relative risk, 0.84; 95% CI, 0.35-2.00).

4.16 Treatment withdrawal

Reason for treatment withdrawal	Budesonide/formoterol group N=437	Budesonide maintenance group N=448
None	378 (86.5)	363 (81.0)
Adverse event	6 (1.4)	14 (3.1)
Treatment increased by health care provider due to unstable asthma	6 (1.4)	11 (2.5)
Investigator safety decision	3 (0.7)	1 (0.2)
Other (advised to cease inhaled glucocorticoids by specialist)	1 (0.2)	0 (0)
Participant decision	20 (4.6)	28 (6.3)
Participant lost to follow up	22 (5.0)	26 (5.8)
Participant pregnancy	1 (0.2)	5 (1.1)
Total treatment withdrawals	59 (13.5)	85 (19.0)

• Table 30: Reasons for treatment withdrawal

A total of 59 participants (13.5%) in the budesonide/formoterol group and 85 participants (19%) in the budesonide maintenance group withdrew during the study, (relative risk 0.71 95% CI 0.52 to 0.97).
20 participants discontinued due to an adverse event. Six participants discontinued the study due to pregnancy. Six participants in the budesonide/formoterol group and 11 in the budesonide maintenance group withdrew from the study due to an increase in treatment due to unstable asthma.

4.17 Adverse events

All patients, N (%)	Budesonide/ formoterol group (N=440)	Budesonide maintenance group (N=448)	Relative risk (95% CI)	P
Patients with at least one AE	385 (87.5)	371 (82.8)	1.06 (1.00 to 1.12)	0.05
Most common AEs (occurring in ≥2% of patients)				
Nasopharyngitis (common cold)	154 (35.0)	144 (32.1)	1.09 (0.90 to 1.31)	0.37
Asthma	87 (19.8)	117 (26.1)	0.76 (0.59 to 0.97)	0.025
Upper respiratory tract infection	77 (17.5)	81 (18.1)	0.97 (0.73 to 1.28)	0.82
Lower respiratory tract infection	45 (10.2)	44 (9.8)	1.04 (0.70 to 1.54)	0.84
Influenza	40 (9.1)	35 (7.8)	1.16 (0.75 to 1.80)	0.49
Sinusitis	27 (6.1)	22 (4.9)	1.25 (0.72 to 2.16)	0.42
Cough	19 (4.3)	27 (6.0)	0.72 (0.40 to 1.27)	0.25
Headache	20 (4.5)	25 (5.6)	0.81 (0.46 to 1.44)	0.48
Viral upper respiratory tract infection	14 (3.2)	18 (4.0)	0.79 (0.40 to 1.57)	0.50
Gastroenteritis	12 (2.7)	19 (4.2)	0.64 (0.32 to 1.31)	0.22
Seasonal allergy	19 (4.3)	10 (2.2)	1.93 (0.91 to 4.11)	0.08
Back pain	19 (4.3)	9 (2.0)	2.15 (0.98 to 4.70)	0.049
Ligament sprain	19 (4.3)	8 (1.8)	2.42 (1.07 to 5.47)	0.028
Oropharyngeal pain	8 (1.8)	14 (3.1)	0.58 (0.25 to 1.37)	0.21
Dysphonia	9 (2.0)	12 (2.7)	0.76 (0.33 to 1.79)	0.53
Viral infection	9 (2.0)	11 (2.5)	0.83 (0.35 to 1.99)	0.68
Diarrhoea	10 (2.3)	8 (1.8)	1.27 (0.51 to 3.19)	0.61
Patients with at least one serious AE (including outcome = death)	28 (6.4)	16 (3.6)	1.78 (0.98 to 3.25)	0.055
Total number of deaths	0 (0)	0 (0)	NA	NA

• Table 31: Summary of adverse events

4.18 Serious adverse events

A total of 44 participants had at least one serious adverse event. The number of ED visits and hospitalizations was five and zero, respectively with budesonide/formoterol and seven and two, respectively with budesonide maintenance. There were no deaths.

All participants experiencing a Serious Adverse Event, N (%)	Budesonide/formoterol group (N=440)	Budesonide maintenance group (N=448)
Abdominal pain	2 (0.5)	0 (0)
Abscess	1 (0.2)	0 (0)
Angina unstable	1 (0.2)	0 (0)
Ankle fracture	1 (0.2)	0 (0)
Appendicitis	1 (0.2)	1 (0.2)
Asthma	0 (0)	1 (0.2)
Atrial flutter	2 (0.5)	0 (0)
Bartholin's abscess	1 (0.2)	0 (0)
Basal cell carcinoma	1 (0.2)	1 (0.2)
Cholelithiasis	0 (0)	1 (0.2)
Diverticulitis	1 (0.2)	0 (0)
Dyspepsia	0 (0)	1 (0.2)
Gastroenteritis	1 (0.2)	0 (0)
Hip fracture	0 (0)	1 (0.2)
Intentional overdose	0 (0)	1 (0.2)
Laceration	0 (0)	1 (0.2)
Meningitis viral	1 (0.2)	0 (0)
Musculoskeletal chest pain	0 (0)	1 (0.2)
Myocardial infarction	1 (0.2)	0 (0)
Myocarditis	1 (0.2)	0 (0)
Nasal polyps	1 (0.2)	0 (0)
Non-cardiac chest pain	1 (0.2)	0 (0)
Pancreatic carcinoma recurrent	1 (0.2)	0 (0)
Papillary thyroid cancer	1 (0.2)	0 (0)
Pneumonia	1 (0.2)	0 (0)
Rectal haemorrhage	1 (0.2)	0 (0)
Renal colic	1 (0.2)	0 (0)
Sinus bradycardia	1 (0.2)	0 (0)
Spinal fusion surgery	1 (0.2)	0 (0)
Supraventricular tachycardia	0 (0)	1 (0.2)
Syncope	0 (0)	1 (0.2)
Talipes	0 (0)	1 (0.2)
Tibia fracture	0 (0)	1 (0.2)
Tonsillitis	1 (0.2)	0 (0)
Transient ischaemic attack	0 (0)	1 (0.2)
Vestibular neuritis	0 (0)	1 (0.2)

- Table 32: Summary of serious adverse events by preferred term and treatment group

5. CHAPTER FIVE: DISCUSSION

5.1 Data published during the course of this research

The SYGMA studies were two large pharmaceutical company funded, international, randomised, double-blind, double-dummy, regulatory trials published in the New England Journal of Medicine in May 2018. [268,269]

In SYGMA 1, published by O'Byrne and colleagues, 3849 patients, aged 12 and older, who were uncontrolled on as required SABA or well-controlled on maintenance ICS and as required SABA and therefore eligible for GINA Step 2 treatment, were randomised to one of three treatment regimens:

1) Twice daily placebo plus terbutaline (0.5mg) as required
2) Twice daily placebo plus budesonide/formoterol (200μg budesonide and 6μg formoterol) as required
3) Twice daily budesonide (200μg) plus as required terbutaline (0.5mg)

All patients underwent a run-in period of two weeks during which they received only terbutaline as required to confirm that GINA Step 2 treatment was appropriate. Patients recorded their peak flow and symptoms and had prompts twice daily to encourage use of the blinded maintenance inhaler.

The primary outcome was the percentage of weeks with well-controlled asthma per patient which was a composite measurement based on as-needed reliever inhaler use, diary data of asthma symptom scores, nighttime awakenings, morning peak expiratory flow and additional inhaled or systemic corticosteroid use. Budesonide/formoterol reliever therapy was superior to terbutaline (34.4% vs 31.1% of weeks, odds ratio, 1.14; 95% CI, 1.00 to 1.30; p=0.046) but inferior to budesonide maintenance (34.3% versus 44.4%, odds ratio, 0.64; 95%CI, 0.57 to 0.73) with regard to the percentage of weeks with well controlled asthma. Changes in asthma control as measured by ACQ-5 questionnaire found in favour of budesonide maintenance versus budesonide-formoterol as needed (mean difference 0.15 95% CI, 0.10 to 0.20) though this fell short of the MCID of 0.5. Of note, measures of asthma control are systematically biased against an as-needed budesonide/formoterol regimen. Traditionally, use of a reliever medication would be included as a marker of symptoms and highlight the need for an escalation in maintenance therapy. With an as-needed budesonide/formoterol regimen the reliever use reflects the amount of preventer delivered.

Budesonide/formoterol used as needed was more effective than SABA, and as effective as budesonide maintenance at reducing the risk of severe exacerbations. The annual rate of severe exacerbations was 0.20 with terbutaline, 0.07 with budesonide/formoterol, and 0.09 with budesonide maintenance; the rate ratio was 0.36 (95% CI, 0.27 to 0.49) for budesonide/formoterol versus terbutaline and 0.83 (95% CI, 0.59 to 1.16) for budesonide/formoterol versus budesonide maintenance.

SYGMA 2, published by Bateman and colleagues, randomised 4215 patients, aged 12 or older, who were assessed as needing GINA Step 2 therapy to either;

1) Twice daily placebo and budesonide/formoterol (200µg budesonide and 6µg formoterol) as required
2) Twice daily budesonide (200µg) plus as required terbutaline (0.5mg)

All patients underwent a run-in period of two weeks during which they received only terbutaline as required to confirm that GINA Step 2 treatment was appropriate. The study included only two mid-trial visits and was therefore less intrusive than the SYGMA 1 study. This would have resulted in participant behaviour which was closer to that seen in the real world.

The primary outcome was the annualised rate of severe exacerbations. Budesonide/formoterol used as needed was non-inferior to budesonide maintenance therapy with regard to the primary outcome of rate of severe exacerbations per year, 0.11 (95% CI, 0.10 to 0.13) in the budesonide/formoterol group versus 0.12 (95% CI, 0.10 to 0.14) in the budesonide maintenance group, rate ratio 0.97 (one-sided 95% confidence upper confidence limit, 1.16). Improvements in asthma control, as measured by ACQ-5 questionnaire, were greater in the budesonide maintenance group than in the budesonide/formoterol as needed group, although the difference of 0.11 fell short of the MCID of 0.5. [53]

These studies both had high internal validity but limited external validity. Both studies required participants to take a twice daily inhaler for 12 months to maintain blinding, so that patients assigned to the budesonide/formoterol as needed group still had to take placebo twice daily. Patients in SYGMA 1 had twice daily prompts to encourage maintenance inhaler use (compliance with maintenance ICS was 84% in SYGMA 1 and 64% in SYGMA 2, compared to rates observed in real-world studies of around 35%)[270] and had to record their asthma symptoms and peak flow. As such, the real-world advantage of using a single inhaler without maintenance treatment was lost and patient selection and behaviour would not have been that seen in usual clinical practice. Both studies also had a run-in period in which ICS was removed to worsen asthma control which would not happen in clinical practice. There was a requirement for participants to be taking SABA more than twice a week to be eligible for enrolment, which would

have excluded patients with intermittent symptoms for whom regular ICS was recommended. The inclusion criteria for the regulatory SYGMA studies were tight and required the subject to demonstrate 12% reversibility in lung function for inclusion. This would have resulted in the exclusion of well-controlled asthmatics with normal spirometry on the day of testing as well as those with chronic airflow obstruction and limited reversibility, suggesting that results are only generalisable to the asthmatic population with suboptimal asthma control and ongoing variable airflow limitation.[248]

The NovelSTART study, also funded by AstraZeneca and published by Beasley and colleagues, overcame the limitations described above and extended these findings to usual clinical practice with an open-label approach and inclusion and exclusion criteria that ensured enrolment of patients representative of those treated for mild asthma in the community. [238] This international, parallel group randomised controlled trial was in 675 adults with mild asthma treated with only as-needed SABA at baseline. Participants were randomised to one of three treatment groups:

1) Albuterol pMDI 100μg two puffs as required for relief of symptoms
2) Budesonide Turbuhaler 200μg one inhalation twice-daily plus as required albuterol via a pMDI
3) Budesonide/formoterol Turbuhaler 200/6μg one inhalation as required for asthma symptoms

In this study, the exacerbation rate was lower with budesonide/formoterol as required compared with albuterol as required (absolute rate 0.195 vs 0.400; relative rate 0.49 (95%CI 0.33-0.72, P<0.001)), and not different from maintenance budesonide plus albuterol as required (absolute rate 0.195 vs 0.175; relative rate 1.12 (0.70-1.79, P=0.65)). Of note, and in contrast to the SYGMA studies, NovelSTART demonstrated fewer severe exacerbations with as-needed budesonide/formoterol than with maintenance budesonide plus as-needed albuterol (relative risk 0.44, 95% CI, 0.20 to 0.96). In other words, the Novel START study identified a 56% lower number of severe exacerbations with budesonide/formoterol reliever therapy than with maintenance budesonide. This difference from the SYGMA studies is most likely to be due to the open-label design of the NovelSTART study which avoided the need for the use of placebo inhalers. Patients taking budesonide/formoterol as needed were not required to use a twice daily placebo inhaler and those taking maintenance budesonide did not have prompts to improve adherence, indeed mean daily adherence to maintenance budesonide was 56% in NovelSTART. Patient behaviour and inhaler use would therefore have more closely reflected usual clinical practice.

With regard to asthma control, maintenance budesonide treatment was superior to budesonide-formoterol as needed. Across all time points, ACQ-5 was lower with as-needed budesonide/formoterol compared with as-needed albuterol (difference -0.15 (95% CI -0.24- 0.06)),

but higher compared with maintenance budesonide plus as-needed albuterol (0.14 (95% CI 0.05-0.23)) though again this is short of the MCID.

A key methodological feature of NovelSTART was that FE_{NO}, a biomarker of T2 inflammation, was measured at baseline and at 12 months. A reduction in FE_{NO} was seen from baseline to 12 months with budesonide maintenance (38 to 25ppb) and with budesonide/formoterol as needed (37 to 26ppb) in this corticosteroid naïve population. At 12 months the geometric mean FE_{NO} in the budesonide/formoterol group was higher than in the budesonide maintenance group (ratio of geometric means 1.13; 95% CI 1.02 to 1.25). These findings confirmed the anti-inflammatory activity of the budesonide-formoterol reliever therapy regimen. The clinical significance of the small differences in FE_{NO} between the regimens at 12 months is not certain, particularly given that the budesonide-formoterol group had a lower risk of severe exacerbations. ATS guidelines would suggest that a change of at least 20% or 10 parts per billion is required to indicate a clinically meaningful decrease in FE_{NO} following an intervention. [34]

5.2 The PRACTICAL, NovelSTART and SYGMA studies

The PRACTICAL study complements the findings of the NovelSTART and SYGMA studies described above.

PRACTICAL extended the population studied to include patients with mild and moderate asthma on maintenance ICS therapy at baseline. In PRACTICAL 70% of participants were taking ICS therapy at baseline, compared with 56% and 54%, in SYGMA 1 and 2 respectively, and this therapy was withdrawn in the SYGMA studies for two to four weeks prior to randomisation. This may account for the higher proportion of participants with a severe exacerbation in the last year in SYGMA 1 and 2 (19.7% and 22%, compared to 12% in PRACTICAL). Mean ACQ was higher in SYGMA 1 and 2, compared with PRACTICAL (1.54, 1.51 and 1.15 respectively). Given that participants in the PRACTICAL study were eligible if they were taking up to 800µg per day budesonide equivalent, it can be concluded that the PRACTICAL population contains partially controlled patients with both mild and moderate asthma, which is important in determining to whom the results apply.

Patients in NovelSTART had less severe asthma than those in both SYGMA and PRACTICAL. Patients were taking only SABA at baseline and half self-reported using SABA less than or equal to twice per

week. This low level of SABA use would have been an exclusion in the final week of run-in for the SYGMA studies. ACQ-5 at baseline was lower (mean ACQ-5 1.1) and there were fewer severe exacerbations in the previous year in participants enrolled in NovelSTART (7.3%) as compared to SYGMA and PRACTICAL. As such, the patients represented in NovelSTART were those for whom initiation of ICS therapy is recommended by the GINA for risk reduction (even if it is not often prescribed or taken).

The regulatory SYGMA studies would have excluded many adults treated for asthma in the community. The PRACTICAL and NovelSTART studies enrolled participants with a doctor's diagnosis of asthma who were also prescribed asthma medications and those with a smoking history, but with exclusion criteria to exclude those with possible COPD. These studies did not have bronchodilator reversibility criteria given its poor sensitivity and specificity criteria for asthma. As such, the findings of these studies are generalisable to adults diagnosed with and prescribed treatment for asthma in the community. [212]

The PRACTICAL study also complements the NovelSTART and SYGMA studies from the point of view of the primary outcome chosen for each. The primary outcome for the NovelSTART study was a composite primary outcome of worsening asthma that included urgent medical review, prescription of systemic glucocorticoids and high beta 2 agonist use (>16 puffs of salbutamol or >eight puffs of budesonide/formoterol), which therefore included exacerbations that did not lead the patient to seek urgent care. The SYGMA 1 study used the percentage of weeks with well-controlled asthma as its primary outcome. Given patients are waiting for symptoms to trigger budesonide/formoterol reliever use, measures of symptom control would be expected to be worse than with maintenance glucocorticoid treatment. The primary outcome used in the PRACTICAL and SYGMA 2 studies of severe exacerbations per patient per year is that recommended by the ERS/ATS task force, relevant both clinically and to the patient. The indication for ICS in mild asthma is to reduce severe exacerbation risk and asthma related death, making this outcome an appropriate primary outcome measure. [9]

The reduction in severe exacerbation rate of 31% (relative rate 0·69, 95% CI 0·48–1·00) with budesonide/formoterol as needed compared to budesonide maintenance and SABA as needed seen in the PRACTICAL study was greater than that seen in SYGMA 1 (rate ratio 0.83, 95% CI 0.59 to 1.16) and SYGMA 2 (rate ratio 0.97 95% CI 0.78 – 1.20) and lower than that seen in the NovelSTART study (relative risk , 0.44; 95% CI, 0.20 to 0.96). While acknowledging the wide confidence intervals in these estimates of risk, these differences may be due to the rigidly controlled setting and regular double dummy placebo inhaler use of the SYGMA studies which would have negated the real-world advantage of a single anti-inflammatory reliever taken only as required to relieve symptoms, and the lower rate of

adherence to maintenance budesonide (76% in PRACTICAL versus 56% in NovelSTART) in the NovelSTART study. The comparative benefit of as-needed budesonide/formoterol seen in the NovelSTART and PRACTICAL studies might have been even greater if adherence was as low as that seen in normal clinical practice.

5.3 What does the PRACTICAL study add?

The PRACTICAL study is the first independently funded randomised controlled trial to compare inhaled corticosteroid-formoterol as sole reliever therapy with maintenance inhaled corticosteroid and SABA reliever therapy in adults with asthma for whom low dose maintenance inhaled corticosteroid therapy was recommended at Step 2 of the GINA strategy (Figures 5 and 7). The study has provided evidence that combination budesonide/formoterol used as needed for symptom relief reduced the rate of severe exacerbations compared with maintenance low dose budesonide plus terbutaline as needed in adults with mild to moderate asthma. The 31% reduction in severe exacerbation risk was achieved with no difference in symptom control.

These results suggest that titrating the dose of inhaled corticosteroid through the as needed use of a combination inhaler that delivers fast-onset LABA simultaneously is more effective for the prevention of severe exacerbations than a maintenance inhaled corticosteroid and as-needed SABA regimen in adults with mild to moderate asthma. The timing of the administration is likely to be a more important determinant of efficacy that the total corticosteroid dose. The as-required regimen allows the patient to up-titrate inhaled corticosteroid at times of increased airways inflammation and allows action to be taken earlier with resolution of symptoms before they become significant enough to require the patient to seek medical intervention.

The co-administration of LABA rather than SABA reliever therapy would also contribute to the reduction in severe exacerbation risk. As reviewed earlier in this thesis and demonstrated nicely by Rabe *et al* in the SMILE study, as-needed formoterol provides better exacerbation control than terbutaline. [211] ICS and LABA have complementary intracellular interactions and effects on airway function. In addition formoterol not only has a bronchodilator action but also immunomodulatory actions in preventing airway oedema, mast cell release of bronchoconstrictors and neutrophil recruitment to the lung and these characteristics may contribute to the reduction in severe exacerbation risk seen with LABAs. [185–189]

The PRACTICAL study findings are consistent with those from trials comparing inhaled corticosteroid-formoterol reliever with SABA reliever in adults with moderate to severe asthma taking maintenance inhaled corticosteroid/LABA combination therapy. A meta-analysis of these studies demonstrated that the use of an inhaled corticosteroid/formoterol reliever reduced the risk of asthma exacerbations compared with SABA reliever (relative risk 0.68 (95% CI 0.58 to 0.80)). It is apparent that the magnitude of the benefit of inhaled corticosteroid-formoterol reliever therapy is similar across the spectrum of asthma severity.

The findings also complement the randomised controlled trial published by Papi and colleagues and discussed in the literature review of this thesis that reported that combination beclomethasone-salbutamol reliever therapy had similar efficacy to maintenance beclomethasone and salbutamol reliever therapy in reducing exacerbation risk. [228]

The PRACTICAL sub-group analysis found that the treatment effect was similar across all patient sub-groups suggesting that the findings are generalisable across the spectrum of mild to moderate asthma, although the greatest absolute benefit will be obtained in those with the greatest morbidity. This result suggests that profiling of baseline characteristics including age, sex, ethnicity, smoking status, baseline ACQ-5, occurrence of severe exacerbations in the previous year, baseline ICS and SABA use and baseline FE_{NO} is not necessary to guide treatment regimen in the setting of mild and moderate asthma. An exception might be for those with high blood eosinophils of $>0.4x10^9/L$, in whom a greater reduction in ACQ-5 was seen with maintenance budesonide than budesonide/formoterol reliever therapy (although this difference and the upper bound of the 95% confidence interval were less than the minimally important clinical difference of 0.5), and there was no significant difference in severe exacerbations.

In contrast, the pooled analysis of the SYGMA studies reported that baseline ICS therapy was a determinant of response to budesonide/formoterol reliever therapy. [271] As-needed budesonide/formoterol was more effective than regular budesonide in those previously on SABA (relative rate 0.74 (95%CI 0.56 to 0.98)), but similar in those previously on ICS (relative rate 1.10 (95% CI 0.86 to 1.41)). In clinical practice, factors such as patient preference and the likelihood of adherence with maintenance ICS could be important in choosing between budesonide-formoterol reliever and daily maintenance inhaled corticosteroid plus as-needed SABA.

An inherent feature of a budesonide/formoterol reliever regimen is that the patient is using it to relieve symptoms, therefore asthma control as measured by the ACQ-5 would be expected to be

worse than with maintenance budesonide. This was the pattern seen in the NovelSTART and SYGMA studies which reported higher ACQ scores with as-needed budesonide/formoterol compared with maintenance budesonide, although the differences of 0.11 to 0.15 were short of the minimum clinically important difference of 0.5. In the PRACTICAL study, however, no difference in ACQ-5 was seen between the groups, with the upper bound of the 95% CI less than a quarter of the MCID for ACQ-5, with the majority of participants having well-controlled asthma with an ACQ5 <1 by the end of the study (mean ACQ at Visit 6, 0.86 (SD 0.75) in the budesonide/formoterol group and 0.80 (SD 0.86) in the budesonide maintenance group). Although the suggestion of poor asthma control is of concern with an as-needed budesonide/formoterol therapy, it seems this is not of clinical significance.

The PRACTICAL study complements data from the NovelSTART study in demonstrating that as-needed budesonide/formoterol has anti-inflammatory activity with the median FE_{NO} falling from 32.5ppb to 24ppb in those who were steroid naïve at baseline in the PRACTICAL study. However, overall, maintenance budesonide demonstrated greater anti-inflammatory activity with a ratio of geometric means of 1.13, which is of unclear clinical significance, particularly given that the rate of severe exacerbations was lower in the group with the higher mean FE_{NO} at 12 months. Furthermore, the ATS guidelines propose that a change of at least 20% and 10 parts per billions is required to indicate a clinically significant change in FE_{NO}. [34]

Across all time points, FEV1 in the budesonide/formoterol group did not differ significantly from the FEV1 in the budesonide maintenance group (mean difference 0.006 litres, 95% CI -0.026 to 0.04) suggesting no short-term loss of lung function in participants using an intermittent ICS regimen.

In summary, the PRACTICAL study demonstrates that as required budesonide/formoterol reduces the risk of severe exacerbation more effectively than maintenance budesonide whilst preventing short-term loss of lung function, mitigating symptoms as effectively as maintenance budesonide and demonstrating anti-inflammatory activity.

5.4 PRACTICAL study limitations

Limitations to the PRACTICAL study included the open-label design which introduced the potential for bias but avoided placebo medication. An open-label design was the only way to investigate the real world advantage of no regular inhaler, and as such patient behaviour in this study is more likely to reflect that seen in usual clinical practice. [272–274] Although participants' usual healthcare providers were aware of the randomised treatment when consulted during an exacerbation, there was no evidence of systematic bias. In the setting of an unplanned medical review, the probability of a participant being prescribed oral corticosteroids for at least 3 days was similar, regardless of treatment group (52 (78%) of 67 with as-needed budesonide–formoterol and 68 (72%) of 94 with budesonide maintenance plus terbutaline).

Study visits were every three months after the first month, and as such patients in the study were getting their asthma reviewed more frequently than they would with their usual medical practitioner.

Reliance on a physician's diagnosis of asthma as a criterion for study inclusion could be considered a strength in that it ensured that participants are representative of the population treated for mild asthma in general practice, but could also be considered a weakness in that the diagnosis of asthma is not always made correctly in primary care. Several studies have demonstrated that between 12 and 50% of patients labelled with difficult to control asthma have a non-asthma diagnosis. [275,276] This misdiagnosis is felt to be due to 'sub-optimal use of relevant diagnostic testing'. Although the participants in this study had mild and moderate rather than difficult to treat asthma, some will have been given an incorrect diagnosis by their GP. The balance in ensuring enrolment of a broad population representative of those treated for mild asthma in the community versus inclusion criteria requiring rigid demonstration of lung function reversibility, with the risk of excluding some of this population, is a difficult one to strike.

The exacerbation and severe exacerbation rate in the study was lower than expected. Despite this, the magnitude of the risk reduction was greater than predicted, and there was sufficient power to identify statistically significant differences in exacerbation rates and severe exacerbation risk, although the confidence intervals were wide with an upper limit of 1.0. In retrospect, this could have been pre-empted. The exacerbation rate chosen was based on the results from three studies. The OPTIMA study, [62] in which 25-29% of severe exacerbations were identified retrospectively based on peak flow, the STAY study, [71] in which all participants had had at least one severe exacerbation in the previous year and the SMILE study, [211] in which all participants had had two or more severe exacerbations in the previous year. Furthermore, the mean baseline FEV1 in the

STAY and SMILE studies was lower than that in PRACTICAL at 72%, suggesting a population with more severe asthma.

The secondary end points have not been adjusted for multiplicity analysis and therefore cannot be used to infer definitive treatment effect. Finally, the greater number of participants who discontinued intervention in the budesonide maintenance group might have favoured this group, as they might have had more exacerbations following withdrawal, but without having consent for follow-up or recording their treatment after withdrawal, it was not possible to determine the magnitude of any such potential bias.

5.5 PRACTICAL study strengths

A considerable strength of the PRACTICAL study is that it is the only independently funded and sponsored study addressing the efficacy of the ICS/fast-onset LABA regimen published to date.

The PRACTICAL study adds a real-world perspective with strong external validity due its broad inclusion criteria and minimal, safety-orientated exclusion criteria. The study included smokers with up to a 20-pack year history with no specific lung function or reversibility requirements. Reversibility criteria would have resulted in the exclusion of well-controlled asthmatics with normal spirometry on the day of testing, as well as exclusion of those with chronic airflow obstruction and limited reversibility. This would have made results generalisable only to the asthmatic population with suboptimal asthma control and ongoing variable airflow limitation.[248]

The primary outcome of the PRACTICAL study was the rate of severe asthma exacerbations per patient per year and therefore focused on risk reduction as suggested by the ATS/ERS outcome measures of clinical trials taskforce report. [2] This is in contrast to the NovelSTART study which had a composite primary outcome and the SYGMA 1 study which used well-controlled asthma weeks as its primary outcome.

All participants were provided with an asthma management plan advising them of how to recognise a deterioration in their asthma. The plan offered advice on when to seek review with their usual medical practitioner and provided space for recording details of the exacerbation. Ongoing asthma management was left with the participant's GP over the year the participant was in the study, as would be the case in usual clinical practice. Participants were not required to fill in a diary every

day or measure their peak flow, if this was not part of their behaviour pre-study, as this could have prompted those randomised to maintenance ICS to take their medication more regularly and promote adherence.

A final strength of the PRACTICAL study was that all participants were clinically phenotyped based on their T2 inflammatory status (eosinophils and FE_{NO}) so that the effect of treatments on airways inflammation, and the relative importance of this profile in the success of the regimen could be determined.

5.6 A role for ICS/fast-onset LABA reliever therapy across spectrum of asthma severity

The PRACTICAL study challenges the need for regular daily ICS in adults with mild/moderate asthma.

It confirms the recommendations made in the Global Initiative for Asthma 2019 strategy and suggests that for the prevention of severe exacerbations, budesonide-formoterol reliever therapy is an alternative, and may be preferred to, maintenance low dose corticosteroids plus SABA reliever at Step 2. [97,98]

A broader case can be made for replacement of SABA with ICS/fast-onset LABA as the suggested default rescue treatment across all severities of asthma, regardless of baseline maintenance treatment, given its superiority in reducing exacerbation risk.[277,278]

The NovelSTART and SYGMA 1 studies have confirmed the superiority of budesonide/formoterol sole reliever therapy to traditional Step 1 treatment with either salbutamol or terbutaline in reducing severe exacerbations and improving asthma control whilst also reducing airways inflammation.[238,279] The available evidence, with the addition of the PRACTICAL study, suggests that as-needed budesonide/formoterol results in at least a similar, if not greater, reduction in exacerbation risk compared to traditional Step 2 maintenance low-dose ICS and SABA reliever with no clinically important difference in asthma control. [238,268,269] This complements findings from randomised controlled trials in adults with moderate to severe asthma (Steps 3, 4 and 5) which have demonstrated that low dose budesonide/formoterol maintenance and reliever therapy is superior to maintenance low and medium/high dose ICS and a SABA reliever in reducing severe exacerbation risk at Step 3,[70,71,206,209,211,221,280] and that medium dose budesonide-formoterol

maintenance and reliever therapy is more effective than maintenance medium and high dose ICS/LABA and SABA reliever therapy at Step 4 and Step 5, respectively.

5.7 How would this work in clinical practice?

At the point of asthma diagnosis as-needed ICS/formoterol would be prescribed. This would reduce the risk of asthma exacerbation and avoid conflicting messages about the role of inhalers and goals of treatment being introduced from the outset. It would also avoid the issues associated with poor adherence with regular ICS in patients with infrequent symptoms, which subsequently expose them to unopposed SABA treatment. For patients with persistent symptoms and exacerbations on this regimen, treatment would be stepped up to low dose maintenance twice daily ICS/formoterol, and the low-dose ICS/formoterol would continue to be used as a reliever as per the MART regimen (Step 3).

If symptoms remained uncontrolled, despite modifiable risk factors having been addressed, treatment could be escalated to maintenance twice daily medium (Step 4) ICS/formoterol, and low dose ICS/formoterol would continue to be used as a reliever as per the maintenance and reliever therapy regimen. After a prolonged period of asthma control and absence of exacerbations, treatment intensity could be stepped down. Across the spectrum of disease severity, as needed low dose ICS/formoterol would be the reliever. Patients already prescribed a twice-daily maintenance ICS regimen, but struggling with adherence and exacerbations could be changed across to this simplified regimen. The point of transition from an as needed only to maintenance and reliever regimen may not necessarily need to be standardised and could be based on patient and doctor preference taking into account frequency of reliever use and whether there had been a recent severe exacerbation. One approach to the transition between treatment steps would be that if the patient was using more than seven actuations a week of budesonide/formoterol for relief of symptoms, two additional daily maintenance actuations would be added. For those who use their budesonide/formoterol reliever between two and seven actuations per week, their treatment could be left at the same level and any maintenance dose could be left unchanged. Those using it less than twice per week could have their maintenance dose reduced a step, but not below as required budesonide/formoterol reliever use. A worsening of asthma requiring a course of systemic corticosteroids would prompt a consideration of a step-up in treatment. Asthma action plans would allow the smooth transition between the treatment levels and would not necessarily require a clinic review once the patient was familiar with the system.

It could be argued that this is an over-simplified approach, but this is deliberate. It makes it universally applicable and provides the minimum that most patients with asthma require across the range of asthma

severity. Consideration of treatable traits, including overlapping disorders, comorbidities, environment and behavioural factors, would continue to trigger changes in treatment.

Of importance is that patients using this regimen can recognise their asthma symptoms and identify them as requiring treatment. Some patients may be insensitive to the perception of airway narrowing and the need to use a bronchodilator. Equally, others may have a tendency to over-perceive relatively minor airways obstruction resulting in medication overuse. There isn't a formal pathway for identifying patients with poor perception of airway obstruction. In the future, technology incorporating electronic monitors to record patterns of inhaler use or performing a methacholine challenge to induce bronchoconstriction and recording a Borg score symptom assessment might be useful in accurately identifying these patients for whom a regular maintenance ICS treatment could be more appropriate.

Equally important to this regimen is that the patient is comfortable with waiting to get asthma symptoms to treat them. This may not be acceptable to patients who have good adherence to maintenance treatment and good asthma control. Many others will find it preferable as a regimen that can be tailored to the variable nature of their symptoms, requires only one device and prevents the need for remembering daily ICS even when they are not experiencing symptoms in order to avoid what is perceived as a remote risk of severe exacerbation.

5.8 Conclusion and future research

In conclusion, budesonide/formoterol used as required for relief of symptoms is more effective at preventing severe exacerbations than maintenance low dose twice daily budesonide plus as-needed terbutaline in adults with mild to moderate asthma.

This study challenges dogma on two fronts. It challenges the necessity for regular inhaled glucocorticoid treatment in mild and moderate asthma, where adherence is a major problem. The study also challenges the long-accepted role of unopposed SABA for relief of acute symptoms and its associated potential long-term adverse effects. This is the first independent randomised controlled trial to highlight the efficacy and safety of alternative options and expands evidence about the generalisability of as-needed ICS/formoterol across the spectrum of mild and moderate asthma regardless of baseline patient characteristics.

This study opens the gateway to further research. Of key importance is whether this regimen is also safe and effective in children. The TREXA[232] and Sumino *et al*[281] studies have investigated as-needed ICS and SABA (beclomethasone and albuterol) in separate inhalers as a reliever in children. There are no studies of as-needed ICS/formoterol as sole therapy in children to date. A larger, international study addressing the efficacy and safety of an as-required ICS/LABA or combination ICS/SABA regimen in children and adolescents is overdue. Other populations in whom this approach would benefit from investigation include pregnant women, in whom a low dose of ICS might be appealing and patients with seasonal allergic asthma.

Would an ICS/SABA reliever combination work just as well as an ICS/LABA reliever combination across the spectrum of asthma severity? ICS/SABA inhalers are available and approved for maintenance use in some areas of the world. It is more than ten years since the BEST study demonstrated the efficacy of a combination ICS/SABA beclomethasone diproprionate/salbutamol reliever inhaler in adults with mild asthma. [228] More recently the BASALT study [234] has demonstrated fewer exacerbations in adults using symptom-guided ICS and SABA in separate inhalers compared with physician-adjusted maintenance ICS treatment. In a longer running, international study with a risk and patient related primary outcome such as exacerbation rate, enrolling patients across the range of asthma severities is a priority to determine if ICS/SABA combination reliever therapies have a better efficacy and safety than salbutamol or terbutaline reliever therapy.

Similarly, further information is required on the efficacy and safety of ICS/fast-onset LABA combination therapies that use ultrafine beclomethasone dipropionate (BDP) or other ICS rather than

budesonide, as it is known that this combination is efficacious in maintenance and reliever therapy.[208] Patients are used to taking SABA reliever therapy through a pMDI, and further evidence of efficacy with budesonide/formoterol 200/6μg and 100/3μg pMDI is a priority to provide the evidence base for this option.

A small proportion of patients have frequent exacerbations but remain asymptomatic between these episodes. Care needs to be taken to identify these people who are more likely to benefit from maintenance therapy. Further work to understand the biology of frequently exacerbating asthma and associated biomarkers is warranted and would be clinically relevant.

All studies in this area to date have been of less than a year duration. There is a need for studies looking at longer term effects of intermittent ICS use on exacerbation risk, airways inflammation and lung function.

The cost of implementing this strategy in low and high income countries requires investigation. The as required regimen has great potential in low income countries where access to ICS-containing medications is limited or non-existent.

Is there a role for the use of an ICS/fast-onset LABA reliever in the setting of acute asthma? Entrenched practice is for the use of salbutamol via nebuliser or MDI and spacer in the acute setting, but there is evidence of similar bronchodilator efficacy of 6μg formoterol to 200μg salbutamol in the emergency department. [282,283] Repeated doses of ICS in acute asthma is associated with improvements in lung function [217] and reduced risk of hospital admission (odds ratio 0.73). [284,285] It is likely that an ICS/fast-onset LABA or SABA combination inhaler may be more efficacious than repeated doses of SABA such as salbutamol, and could be recommended for use in addition to the administration of systemic corticosteroids in the ED treatment of severe exacerbations of asthma. [285]

The ICS/formoterol reliever therapy regimen represents a paradigm shift and the most fundamental change in the management of asthma in the past 20 years. It has the potential to revolutionise asthma management and the experience of patients with asthma.

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Appendix 1: ANZCTR registration

ANZCTR
Australian New Zealand Clinical Trials Registry

LOG OFF Logged in as Joanna Hardy [Account details]

DEFINITIONS HINTS AND TIPS FAQs REGISTER TRIAL MY TRIALS

Register a trial

Please note that the ANZCTR website will be unavailable from 1pm until 2pm (AEST) on Monday 29th April for website maintenance. Please be sure to log out of the system in order to avoid any loss of data. Thank you and apologies for any inconvenience caused.

Acknowledgment | Step 1: Titles & IDs | Step 2: Health condition | Step 3: Intervention/exposure
Step 4: Outcomes | Step 5: Eligibility | Step 6: Study design | Step 7: Recruitment
Step 8: Funding & Sponsors | Step 9: Ethics & Summary | Step 10: Contacts | Step 11: Data sharing statement
Step 12: Summary Results | Review & Submit

Request number	370122
Current page	Review

< BACK SUBMIT

Registration number	ACTRN12616000377437
Ethics application status	Approved
Date submitted	18/03/2016
Date registered	23/03/2016
Type of registration	Prospectively registered

Titles & IDs

Edit step 1

Public title	Randomised Controlled Trial of the efficacy and safety of an Inhaled Corticosteroid and Long Acting Beta Agonist reliever therapy regimen in asthma
Scientific title	A 52-week, open label, parallel group, multicentre, phase III, randomised controlled trial to compare the efficacy and safety of Budesonide/formoterol turbuhaler taken as required for relief of symptoms and Budesonide turbuhaler as maintenance and terbutaline turbuhaler as required for relief of symptoms of asthma in adults.
Secondary ID [1]	None known
Universal Trial Number (UTN)	U1111-1174-2273
Trial acronym	PRACTICAL: PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist
Linked study record	

Health condition

Edit step 2

Health condition(s) or problem(s) studied:

Asthma

Condition category	Condition code
Respiratory	Asthma

Intervention/exposure

Edit step 3

Study type	Interventional
Description of intervention(s) / exposure	Inhaled corticosteroid/Long acting beta Agonist (ICS/LABA) reliever therapy: budesonide/formoterol turbuhaler 200micrograms/6micrograms taken one inhalation for relief of symptoms as required for 52 weeks. These participants will receive no maintenance therapy. In the electronic monitor sub-study, 110 patients will have an electronic monitor incorporated into each turbuhaler device to record the date and time of actuations to allow a detailed assessment of patterns of use of randomised treatments. 55 participants will be recruited from the ICS/LABA reliever group and 55 participants from the maintenance ICS and SABA reliever therapy group. This substudy will run for 52 weeks. Inhaler use will be monitored electronically. An electronic monitor device will be attached to each inhaler, which is able to measure the date and time of each actuation performed.
Intervention code [1]	Treatment: Drugs
Comparator / control treatment	Maintenance Inhaled Corticosteroid (ICS) and Short Acting Beta Agonist (SABA) reliever therapy; budesonide Turbuhaler 200 micrograms, 1 inhalation twice daily and terbutaline metered dose inhaler 250 micrograms 2 inhalations for relief of symptoms as required, for 52 weeks. In the electronic monitoring sub-study, inhaler use will be monitored electronically. An electronic monitor device will be attached to each inhaler, which is able to measure the date and time of each actuation performed. The electronic monitoring sub-study will run for 52 weeks.
Control group	Active

Outcomes

Edit step 4

Primary outcome [1]	The primary outcome variable is severe asthma exacerbation rate expressed as number of exacerbations per patient per year.
Timepoint [1]	Timepoint is determined by occurrence of either the use of systemic corticosteroids for at least 3 days because of asthma, or Hospitalisation or emergency department (ED) visit because of asthma, requiring systemic corticosteroids These criteria will be determined from participant self report. Asthma exacerbations will be assessed throughout the 52 week intervention period
Secondary outcome [1]	Time to first severe exacerbation of asthma, which is defined as either the use of systemic corticosteroids for at least 3 days because of asthma, or Hospitalisation or emergency department (ED) visit because of asthma, requiring systemic corticosteroids. This outcome will be assessed by participant self report at interview. Participant NHI number will be used to centrally validate exacerbation outcome data relating to hospital attendance and/or admission.
Timepoint [1]	This outcome measure is measured from date intervention commenced, to the date first severe exacerbation begins.
Secondary outcome [2]	Asthma Control Questionnaire score (ACQ-5 score), as measured by the ACQ-5 validated questionnaire completed by the participant
Timepoint [2]	Weeks 0, 4, 16, 28, 40 and 52
Secondary outcome [3]	On-treatment Forced Expiratory Volume in 1 second (FEV1) percentage predicted, as measured by spirometry assessment. Percentage predicted values will be obtained for each participant from height, age and ethnicity recorded as part of demographics and processed according to Quanjer et al 2012
Update	On-treatment Forced Expiratory Volume in 1 second (FEV1) (litres), as measured by spirometry assessment.
Reason	Percentage predicted removed from outcome variable, as change in FEV1 in litres will be reported.
Timepoint [3]	Weeks 0, 4, 16, 28, 40 and 52
Secondary outcome [4]	Fractional Exhaled Nitric Oxide, as measured by a NIOX VERO device
Timepoint [4]	Weeks 0, 16 and 52
Secondary outcome [5]	Mean Inhaled Corticosteroid dose per day (budesonide micrograms/day), as recorded by the electronic monitor devices on nested substudy inhalers
Timepoint [5]	Data collected over duration of study using electronic monitors, and will be assessed week 0 to 52.
Secondary outcome [6]	Proportion of patients with at least one day of no inhaled corticosteroid use, as recorded by the electronic

	monitors on inhalers in nested sub study
Timepoint [6]	Duration of study; week 0 to 52.
Secondary outcome [7]	Longest duration of no inhaled corticosteroid use, as recorded by the electronic monitors on inhalers in nested substudy
Timepoint [7]	Duration of study; week 0 to 52.
Secondary outcome [8]	Total systemic corticosteroid exposure. In the nested sub-study, systemic corticosteroid exposure/year in which the total inhaled Corticosteroid dose/year (as recorded by the electronic monitors on each inhaler)is converted to oral prednisone-equivalent dose and added to the participant self-reported oral corticosteroid use.
Timepoint [8]	Duration of study; week 0 to 52
Secondary outcome [9]	To examine patient attitudes to the treatment regimens through the validated belief about medicines questionnaire.
Timepoint [9]	Week 0 and 52
Secondary outcome [10]	To determine whether baseline socioeconomic characteristics such as housing status predict preferential response to randomised treatment through completion of Housing status questionnaire.
Timepoint [10]	Week 0
Secondary outcome [11]	Proportion of participants with at least one episode of high use, defined as greater than 16 actuations of Terbutaline in a 24 hour period, or greater than 8 actuations of budesonide/formoterol in a 24 hour period, as recorded by the electronic monitors on inhalers in the nested sub-study.
Timepoint [11]	Duration of study; week 0 to 52.
Secondary outcome [12]	Number of days of high beta agonist use, defined as greater than 16 actuations of Terbutaline in a 24 hour period, or greater than 8 actuations of budesonide/formoterol in a 24 hour period, as recorded by the electronic monitors on inhalers in the nested sub-study
Timepoint [12]	Duration of stud; week 0 to 52.
Secondary outcome [13]	Number of days of high use without medical review within 48 hours, in participants with at least one high use episode, as recorded by the electronic monitors on inhalers in the nested substudy. Medical review will be assessed by participant self-report.
Timepoint [13]	Duration of study; week 0 to 52.
Secondary outcome [14]	Maximum number of beta agonist actuations in a 24 hour period as recorded by the electronic monitors on inhaler in the nested substudy.
Timepoint [14]	Duration of study; week 0 to 52.
Secondary outcome [15]	For the rate of exacerbations (measured by self report) a differential effect of treatment will be explored with each of the following baseline moderating variables: Short Acting Beta Agonist (SABA) use (measured as the average number of occasions per week of self-reported SABA use in the four weeks before enrolment), whether there has been a severe exacerbation in the year prior to enrolment (measured by participant self-report), age (measured by self-report), sex (measured by self-report), smoking status (measured by self report), baseline Asthma Control Questionnaire-5 (ACQ-5) score (measured by ACQ-5 score), Fractional Exhaled Volume in 1 second (FEV1) percent predicted (measured by predicted values based on self reported height, age and ethnicity), Fractional Exhaled Nitric Oxide (FeNO, measured by NIOX VERO device), blood eosinophil count (measured by laboratory test), serum periostin level (measured by laboratory test) and T helper cell 2 (Th2) status (a Th2 score based on tertiles for each baseline measure of blood eosinophil count, FeNO and serum periostin.)
Update	For the rate of exacerbations (measured by self report) a differential effect of treatment will be explored with each of the following baseline moderating variables: Short Acting Beta Agonist (SABA) use (measured as the average number of occasions per week of self-reported SABA use in the four weeks before enrolment), ICS stratum at baseline (measured as the self-reported use of ICS within the 3 months before enrolment), ICS adherence at baseline, in those using ICS at baseline, measured as the average self-reported adherence per day, within the four weeks before enrolment with self-reported adherence measured as a proportion of the prescribed dose, smoking status at baseline, whether there has been a severe exacerbation in the year prior to enrolment (measured by participant self-report), age (measured by self-report), sex (measured by self-report), smoking status (measured by self report), baseline Asthma Control Questionnaire-5 (ACQ-5) score (measured by ACQ-5 score), Fractional Exhaled Volume in 1 second (FEV1) percent predicted (measured by predicted values based on self reported height, age and ethnicity), Fractional Exhaled Nitric Oxide (FeNO, measured by NIOX VERO device), blood eosinophil count (measured by laboratory test),
Reason	Removal of Periostin as this was only collected in a sub-group of participants. . Addition of ICS stratum at baseline and ICS adherence at baseline. Omitted in error. Important to consider baseline steroid use.
Timepoint [15]	Duration of study; week 0 to 52.
Secondary outcome [16]	The proportion of exacerbations defined by the use of systemic corticosteroids for at least 3 days because of asthma, and the proportion defined by the requirement for Hospitalisation or emergency department (ED) visit because of asthma, requiring systemic corticosteroids.

Timepoint [16]	Weeks 0, 4, 16, 28, 40 and 52
Secondary outcome [17]	The proportion of patients with at least one severe exacerbation. This outcome will be assessed by participant self report at interview. Participant NHI number will be used to centrally validate exacerbation outcome data relating to hospital attendance and/or admission.
Timepoint [17]	Weeks 0, 4, 16, 28, 40 and 52
Secondary outcome [18]	Proportion of participants withdrawn and reason. The Proportion of participants withdrawn due to "treatment failure" will also be presented. Treatment failure is defined as withdrawal due to uncontrolled asthma under the randomised regimen resulting in safety concerns, as judged by the investigator or if randomised treatment is modified by the participant's GP or other healthcare provider Data is measured from self-report by participant
Timepoint [18]	Date of withdrawal
Secondary outcome [19]	Cost effectiveness will be calculated for each treatment regimen (medications, emergency medical attention, ED visits, hospital admissions and non medical costs including days off work). 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). The cost-effectiveness data collected will allow extrapolation to future pricing models with lower cost generic medications. This outcome data will be assessed by participant self report at interview. Participant NHI number will be used to centrally validate data relating to hospital attendance and/or admission.
Timepoint [19]	Duration of study; week 0 to 52.
Secondary outcome [20]	Proportion of participants with at least one episode of marked beta agonist overuse, defined as greater than 24 actuations of Terbutaline in a 24 hour period, or greater than 12 actuations of budesonide/formoterol in a 24 hour period, as recorded by the electronic monitors on inhalers in the nested sub-study.
Timepoint [20]	Duration of study; week 0 to 52.
Secondary outcome [21]	Number of days of high beta agonist use, defined as greater than 16 actuations of Terbutaline in a 24 hour period, or greater than 8 actuations of budesonide/formoterol in a 24 hour period, as recorded by the electronic monitors on inhalers in the nested sub-study
Timepoint [21]	Duration of study; week 0 to 52.
Secondary outcome [22]	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 a least one marked beta agonist use episode. Where marked beta agonist use is defined as greater than 24 actuations of Terbutaline in a 24 hour period, or greater than 12 actuations of budesonide/formoterol in a 24 hour period, as recorded by the electronic monitors on inhalers in the nested sub-study.
Timepoint [22]	Duration of study; week 0 to 52.
Secondary outcome [23]	[New secondary outcome]
Update	Rate of asthma exacerbations per patient per year
Reason	In error not included in initial entry
Timepoint [23]	[New secondary outcome]
Update	This is defined as worsening asthma resulting in unplanned medical review (primary care visit, ED visit or hospital admission) and/or worsening asthma resulting in the use of systemic corticosteroids, such as a course of oral prednisone for any duration. This outcome will be assessed by participant self report at interview
Reason	In error not included in initial entry
Secondary outcome [24]	[New secondary outcome]
Update	Time to first exacerbation of asthma
Reason	In error not included in initial entry
Timepoint [24]	[New secondary outcome]
Update	This is defined as worsening asthma resulting in unplanned medical review (primary care visit, ED visit or hospital admission) and/or worsening asthma resulting in the use of systemic corticosteroids, such as a course of oral prednisone for any duration. This outcome will be assessed by participant self report at interview
Reason	In error not included in initial entry

Eligibility

Edit step 5

Key inclusion criteria	Adults aged 18 to 75 years. Self-report of a doctor's diagnosis of asthma. Not used Inhaled corticosteroids in the 12 weeks prior to entry into the study and suffering from asthma symptoms or Need for SABA on two or more occasions in the last 4 weeks, or Waking due to asthma once or more in the last 4 weeks, or Exacerbation requiring oral corticosteroids in the last 52 weeks Or has used inhaled corticosteroids in the 12 weeks prior to entry in the study, and is prescribed ICS at low or moderate doses (<500micrograms/day fluticasone propionate or small particle formulation beclomethasone diproprionate (QVAR); 800 micrograms/day budesonide; 1,000 micrograms/day beclomethasone diproprionate (Beclazone)), and: i. has partly or well controlled asthma as defined by GINA guidelines OR ii. has uncontrolled asthma as defined by GINA guidelines and either poor adherence to ICS and/ or unsatisfactory inhaler technique. Willing and able to give informed consent for participation in the trial. In the investigator's opinion, able and willing to comply with all trial requirements. Willing to allow their GP (and specialist if appropriate) to be notified of participation in the trial.
Minimum age	18 Years
Maximum age	75 Years
Gender	Both males and females
Can healthy volunteers participate?	No
Key exclusion criteria	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. Self-reported past admission to the Intensive Care Unit (ICU) with life-threatening asthma (representing patients at highest risk of adverse asthma outcomes). Self-reported treatment with oral prednisone or other systemic corticosteroids in the six weeks before potential study entry (representing recent unstable asthma). A home supply of prednisone for use in worsening asthma, as part of a current asthma plan. Self-reported diagnosis of COPD, bronchiectasis or interstitial lung disease. Self-reported greater than 20 pack year smoking history, or onset of respiratory symptoms after the age of 40 years in current or ex-smokers with more than or equal to a 10 pack year history. Self-reported current pregnancy or breast feeding at the time of enrolment or planned pregnancy within the study period. Unwilling or unable to switch from current asthma treatment regimen. 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).

Study design

Edit step 6

Purpose of the study	Treatment
Allocation to intervention	Randomised controlled trial
Procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)	The central electronic Case Report Form (eCRF) system will perform randomisation. It will conceal the allocations and will release a participant's randomisation outcome only at the time of randomisation. The randomisation schedule will not be accessed by study staff.
Methods used to generate the sequence in which subjects will be randomised (sequence generation)	A computer-generated randomisation number sequence will be created by the study statistician, independent of the investigators undertaking recruitment and subsequent visits. Participants will be block randomised.

Randomisation will be stratified according to whether participants used ICS therapy prior to enrolment or not.
A computer-generated randomisation number sequence will be created by the study statistician, independent of the investigators undertaking recruitment and subsequent visits.

Masking / blinding Open (masking not used)

Who is / are masked / blinded?

Intervention assignment Parallel

Other design features

Phase Phase 3

Type of endpoint(s) Safety/efficacy

Statistical methods / analysis

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.

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
Simple t-tests by time of measurement and mixed linear models for repeated measures by time for ACQ-5 score, FEV1 , FEV1 percentage predicted, 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.

The Work Productivity Activity impairment Asthma questionnaire 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 consists of five sub-scores and 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.

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 previous randomised controlled trials which have reported a rate of 0.21 in steroid-naïve subjects treated with budesonide 200micrograms/day, (using the same criteria for severe exacerbations, peak flow criteria excluded) and rates in subjects previously treated with ICS at baseline of 0.92 and 0.96 (budesonide 200 and 400micrograms/day), 0.35 (budesonide 800micrograms/day), and 0.35 (budesonide 400micrograms/day). 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, and a non-significant 38% reduction in severe exacerbations with ICS and SABA reliever therapy (separate inhalers) vs physician-adjusted maintenance ICS. This 38% reduction in severe exacerbations 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 substudy 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% of their prescribed ICS dose.

Recruitment

Edit step 7

Recruitment status Active, not recruiting

Update Completed

Reason Tthe study has concluded normally. Follow-up and data collection are complete)

Date of first participant enrolment

Anticipated	5/04/2016	**Actual**	4/05/2016

Date of last participant enrolment

Anticipated	1/11/2017	**Actual**	22/12/2017

Date of last data collection

Anticipated	22/12/2018	**Actual**	
		Update	21/12/2018
		Reason	Up to date data

Sample size

Target	890	**Accrual to date**		**Final**	890

Recruitment outside Australia

Country [1]	New Zealand
State/province [1]	Wellington
Country [2]	New Zealand
State/province [2]	Auckland
Country [3]	New Zealand
State/province [3]	Tauranga
Country [4]	New Zealand
State/province [4]	Rotorua

Funding & Sponsors

Edit step 8

Funding source category [1]	Government body
Name [1]	Health Research Council of New Zealand
Address [1]	Level 3 - ProCARE Building, Grafton Mews, at 110 Stanley Street, Auckland 1010
Country [1]	New Zealand
Primary sponsor type	Other
Name	Medical Research Institute of New Zealand
Address	Level 7 CSB Building Wellington Hospital Riddiford Street Newtown Wellington 6021
Country	New Zealand
Secondary sponsor category [1]	None
Name [1]	
Address [1]	
Country [1]	

Ethics approval

Edit step 9

Ethics application status	Approved
Ethics committee name [1]	Northern B Health and Disability Ethics Committee
Ethics committee address [1]	Ministry of Health Ethics Department Freyberg Building Reception – Ground Floor 20 Aitken Street Wellington 6011
Ethics committee country [1]	New Zealand
Date submitted for ethics	

Audit Trail Report

Date	User	Document	Action	Details
26 Apr 2019 11:56:043-0700	Rebecca Kunder		Started	The custodian composed the ePak succesfully. User UUID : 84caccc6-12e1-43d3-b61c-49d514c48bb2
26 Apr 2019 11:56:043-0700	Rebecca Kunder		RequestSent	Sign request sent to ePak recipient. User UUID : 84caccc6-12e1-43d3-b61c-49d514c48bb2
26 Apr 2019 11:57:035-0700	Rebecca Kunder	GA41024 Protocol Clarification Letter 4.pdf	Signed	The recipient signed the document with no comments. Comments: None Reason: I am the author of this document. User UUID : 84caccc6-12e1-43d3-b61c-49d514c48bb2 Document UUID : c9ef3ebb-ea6f-44b8-ad1c-4370eac4631d
26 Apr 2019 11:57:035-0700	Rebecca Kunder		Completed	The ePak completed the workflow successfully custodian. User UUID : 84caccc6-12e1-43d3-b61c-49d514c48bb2

Appendix 2: Ethics Committee Approval

Health and Disability Ethics Committees
Ministry of Health
Freyberg Building
20 Aitken Street
PO Box 5013

Wellington
6011

0800 4
ETHICS
hdecs@moh.g
ovt.nz

18 November 2015

Prof Richard Beasley

Dear Prof Beasley

Re:	Ethics ref:	15/NTB/178
	Study title:	Randomised Controlled Trial of an Inhaled Corticosteroid and LongActing Beta Agonist Reliever Therapy Regimen in Asthma.

I am pleased to advise that this application has been approved by the Northern B Health and Disability Ethics Committee. This decision was made through the HDEC-Full Review pathway.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study's sponsor, to ensure that these conditions are met. No further review by the Northern B Health and Disability Ethics Committee is required.

Standard conditions:

1. Before the study commences at any locality in New Zealand, all relevant regulatory approvals must be obtained.

2. Before the study commences at any locality in New Zealand, it must be registered in a WHO-approved clinical trials registry (such as the Australia New Zealand Clinical Trials Registry, www.anzctr.org.au).

3. Before the study commences at a given locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

After HDEC review

Please refer to the Standard Operating Procedures for Health and Disability Ethics Committees (available on www.ethics.health.govt.nz) for HDEC requirements relating to amendments and other post-approval processes.

Your next progress report is due by 17 November 2016.

Participant access to ACC

The Northern B Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation (ACC).

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

Raewyn Sporle
Chairperson
Northern B Health and Disability Ethics Committee

Encl: appendix A: documents submitted appendix B: statement of compliance and list of members

Appendix A
Documents submitted

Document	Version	Date
CV for CI: CV: Prof Richard Beasely	1.0	14 July 2014
CVs for other Investigators: CV: Dr Steve McKinstry	1.0	31 May 2015

CVs for other Investigators: CV: Dr Janine Pilcher	1.0	01 September 2015
Evidence of CI indemnity	1.0	01 February 2015
Evidence of scientific review: Peer Review: Note to File	1.0	16 September 2015
Investigator's Brochure: Datasheet: Bricanyl	1.0	12 November 2014
Investigator's Brochure: Datasheet: Pulmicort	1.0	04 March 2013
Investigator's Brochure: Datasheet: Symbicort	1.0	04 March 2013
Survey/questionnaire: Beliefs about Medicines Questionnaire	1.0	16 September 2015
Survey/questionnaire: Asthma Control Questionnaire (ACQ-5)	1.0	30 November 2001
Asthma Action Plan: ICS/LABA Peak Flow	1.0	12 August 2015
Asthma Action Plan: ICS/LABA	1.0	12 August 2015
Asthma Action Plan: ICS and SABA Peak Flow	1.0	12 August 2015
Asthma Action Plan: ICS and SABA	1.0	12 August 2015
PIS/CF: Withdrawal of Consent Form	1.0	16 September 2015
GP to Patient Letter	1.0	16 September 2015
Inhaler use information: ICS and SABA (Electronic monitor)	1.0	16 September 2015
Inhaler use information: ICS and SABA (Non-Electronic monitor)	1.0	16 September 2015
Inhaler use information: ICS/LABA (Electronic monitor)	1.0	16 September 2015
Inhaler use information: ICS/LABA (Non-Electronic monitor)	1.0	16 September 2015
Participant Card	1.0	16 September 2015
PIS/CF: PIS-CF	1.0	16 September 2015
Protocol: PRACTICAL Protocol	1.0	16 September 2015
Other (No Description Entered)	1	17 September 2015
PIS/CF: PIS-CF V2.0 Clean	2.0	16 October 2015
PIS/CF: PIS-CF V2.0 Tracked Changes	2.0	16 October 2015
Provisional Approval Letter of Response	1.0	30 October 2015

Appendix B
Statement of compliance and list of members

Statement of compliance

The Northern B Health and Disability Ethics Committee:

- is constituted in accordance with its Terms of Reference
- operates in accordance with the Standard Operating Procedures for Health and Disability Ethics Committees, and with the principles of international good clinical practice (GCP)
- is approved by the Health Research Council of New Zealand's Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990
- is registered (number 00008715) with the US Department of Health and Human Services' Office for Human Research Protection (OHRP).

List of members

Name	Category	Appointed	Term Expires
Mrs Raewyn Sporle	Lay (the law)	01/07/2012	01/07/2015
Mrs Maliaga Erick	Lay (consumer/community perspectives)	01/07/2012	01/07/2015
Mrs Phyllis Huitema	Lay (consumer/community perspectives)	19/05/2014	19/05/2017
Dr Nora Lynch	Non-lay (health/disability service provision)	01/07/2015	01/07/2018
Miss Tangihaere Macfarlane	Lay (consumer/community perspectives)	19/05/2014	19/05/2017
Mrs Kate O'Connor	Non-lay (other)	01/07/2012	01/07/2015
Mrs Stephanie Pollard	Non-lay (intervention studies)	01/07/2012	01/07/2015

Unless members resign, vacate or are removed from their office, every member of HDEC shall continue in office until their successor comes into office (HDEC Terms of
Reference)

http://www.ethics.health.govt.nz

Appendix 3: Participant information sheet and consent form

Participant Information Sheet

Study title:	**PRACTICAL: PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist**		
Locality:	**MRINZ**	Ethics committee ref.:	**15/NTB/178**
Lead investigator:	**Prof Richard Beasley**	Contact phone number:	**04 805 0147**

INTRODUCTION

You are invited to take part in a research study on the effectiveness of two different inhaler regimens, for people with asthma who are aged between 18 and 75. Asthma is a major health problem globally and New Zealand in particular has high rates of asthma. At the moment, we are unsure which regimen is most beneficial for patients with asthma, which is why we are conducting this trial. If you choose to take part, you will be randomised to receive one of the following regimens, for one year:

1. Symbicort inhaler, for relief of symptoms, when you need it (Symbicort regimen)
2. Regular "preventer" Pulmicort inhaler and Bricanyl inhaler, for relief of symptoms, when you need it (Pulmicort and Bricanyl regimen)

You will have a 1 in 2 chance of receiving either regimen. The Study Doctor will not know which regimen you will be given until it is time for them to give you your study inhalers. More information about these regimens can be found on page 2.

In total 890 patients with asthma will be recruited from sites around New Zealand. Your participation is entirely voluntary (your choice). Your decision whether or not to participate will not affect your health care in any way or your future relationship with the hospital or your GP.

If you are pregnant, have ever been to ICU with Asthma or require higher levels of treatment, you will not be eligible to take part in the study.

This study has been designed by doctors interested in finding out which inhaler regimen works best. It is funded by the Health Research Council of New Zealand. The Medical Research Institute of New Zealand (MRINZ) are sponsoring (co-ordinating) the study and it has been approved by the Northern B Health and Disability Ethics Committee.

If you have any questions about the study please feel free to contact one of the Study Doctors. Their details are included on page 9. This document is 11 pages long, including the Consent Form. Please make sure you have read all the pages. If you require an interpreter, this will be arranged.

The Study Regimens:

Regimen	What inhalers are given and why?	When would I take the inhaler(s)?	What is the inhaler like?		Is this regimen currently used by asthma patients?
Symbicort	Symbicort inhaler This contains: - a beta- agonist to quickly open up the airways - a steroid to reduce airway inflammation	When I have symptoms	This is a turbuhaler. Use involves twisting a knob at the base and taking a forceful breath in to inhale the medication.		No, this is a new regimen, although the Symbicort turbuhaler is commonly used in NZ according to other regimens.
Pulmicort and Bricanyl	Bricanyl inhaler This contains a beta- agonist to quickly open up the airways	When I have symptoms	This is a turbuhaler. Use involves twisting a knob at the base and taking a forceful breath in to inhale the medication.		Yes, both are often given to patients with mild asthma to use in these ways.
	Pulmicort inhaler This contains a steroid to reduce airway inflammation	Morning and night	This is a turbuhaler. Use involves twisting a knob at the base and taking a forceful breath in to inhale the medication.		

You will be given a written Asthma Action Plan to help you understand how to take your inhalers and when to seek medical help if your asthma worsens. If you regularly use a peak flow meter to help you manage your asthma, you will be able to continue doing this throughout the study. You will also be given information about how to care for your inhalers and when to contact one of the Study Doctors. We will inform your GP that you have been enrolled in the study.

Visits 2-5 (4, 12, 24 and 36 weeks after Visit 1)

At these visits we will check your inhaler technique, supply you with new inhalers, get you to complete the ACQ-5 and ask you how your health has been since the last visit. At Visit 3 we will also repeat the fraction of exhaled nitric oxide test, spirometry measurement and ask you to complete the WPAI-Asthma again. Each visit should take between 30 and 60 minutes.

Visit 6 (52 weeks after Visit 1, unless you withdraw or are withdrawn earlier for safety reasons)

This will be your final visit. We will check your inhaler technique and ask you to complete the ACQ-5, BMQ and WPAI-Asthma questionnaires again. We will ask you to describe your job if you are employed. We will also ask you to complete three other questionnaires which help us to understand your health and how your asthma affects your life: the Asthma Quality of Life Questionnaire (AQLQ-S), the EQ-5D-5L and the Valuation of Lost Productivity (VOLP) questionnaire. We will also get you to perform the fraction of exhaled nitric oxide test and spirometry again. We will ask you how your health has been since the last visit.

The decision of what asthma inhalers you will have after the study will depend on your usual GP. We will inform your GP that you have completed the trial. This visit will take approximately one hour.

Between Visits

Between visits you will be under the care of your usual GP. Should you need to seek medical assistance for your asthma, please go to your usual health care provider (GP, after hours or hospital as appropriate). You will be treated in accordance with standard clinical care.

Please do not contact the Study Doctor for medical assistance as they are required to direct you to your usual health care provider. You will be given a list of circumstances where you are asked to contact the Study Doctor. They will be available to take your call/email during business hours, Monday to Friday.

If you become pregnant or there is concern about your health or wellbeing during the study you will be withdrawn from the study by the Study Doctor. This will be discussed with you at an Unscheduled Visit (see below).

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

Initial visit

There will be an initial visit to explain the study and for you to provide your written informed consent to participate. This visit should take between 30 and 60 minutes. We will collect information about your health to check whether you are eligible to take part in the study. If you are eligible to take part we will perform Visit 1 either immediately after this check, or on another day if more convenient for you.

Visit 1

We will ask you to fill in three short written questionnaires about your asthma; these are the Asthma Control Questionnaire (ACQ-5), the Beliefs about Medicines Questionnaire (BMQ) and the Work Productivity and Activity Impairment Questionnaire (WPAI-Asthma). These questionnaires include questions about your symptoms, how you find using your medication and how asthma affects your work or study and will take 20 minutes or so to complete. We will also ask you questions about your housing status and collect your address, which will be sent to the sponsor (MRINZ). We will also ask for your national health index (NHI) number to verify your hospital admissions data against Ministry of Health records. Your height and weight will be recorded.

We will measure your fractional exhaled nitric oxide levels (a gas you normally breathe out). This is a simple test involving breathing into a mouthpiece and gives information about inflammation in your lungs. We will also measure spirometry. This involves blowing forcefully into a tube. This gives us information about how your lungs are working. Some people feel light headed after performing spirometry, this resolves quickly and you will be able to stop at any time.

A blood test will be taken, to measure the following:

- Full Blood Count

This blood test is being done to give us information about your asthma and will be the only blood test required in the study. We will take around 4mls of blood in total, however in some cases we may require extra samples, for example to re-do a test that could not be analysed.

A local laboratory will analyse your full blood count and will destroy the sample as per their standard procedure, once the result is known.

You will then be assigned one of the inhaler regimens. We will collect all of your usual inhalers and provide you with the study ones. We will provide information on how to use the inhalers and check your inhaler technique.

It is important that while you are on the trial you only use the inhalers you have been allocated (unless directed otherwise by a doctor) and do not share your inhalers.

Unscheduled Visits

You may be asked to attend an additional study visit to check how you are and collect your inhalers if:

- We have concerns around your safety to continue in the study
- You are concerned you will run out of your inhaler medication before the next scheduled visit or any of your inhalers are not operating correctly
- You wish to withdraw from the study

This visit will take approximately 30 minutes.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

Risks

Risk of poor asthma control

We are uncertain which of the regimens will provide the best treatment for your asthma. It is possible that, given your asthma symptoms, you might be allocated to a different regimen from that used by your doctor, based on the current guideline recommendations. All inhalers used in this study have been used for the treatment of asthma in New Zealand and internationally for decades.

We will be checking very carefully that your asthma is not too severe for you to take part in this study. However, once you are enrolled in the study, the chance of you being allocated to a particular regimen will not be based on your asthma symptoms, it will be by chance.

If you or the Study Doctor are concerned about your asthma control you may be withdrawn from the study for your safety. You would be referred back to your GP who would take back responsibility for your treatment, based on your symptoms and other medical history.

Risk of medication side effects

The study inhalers have been used for the treatment of asthma for decades and are commonly prescribed for the treatment of asthma, around the world.

The following are the known potential side-effects of the study inhalers, but these generally occur at higher doses than those given in the study. Please discuss with the Study Doctor if you are uncertain as to what the terms below mean:

Bricanyl:

Tremor, headache, increased heart rate (heart beating fast), muscle cramps, irregular heart rhythms, nervousness, low levels of potassium in the blood.

Rarely, some people may experience occasional extra heart beats, vomiting, bad taste, diarrhoea, sweating, muscle twitching, drowsiness, dizziness, sleep disturbances and behavioural disturbances such as agitation, hyperactivity and restlessness, skin rashes and plaques.

Symbicort:

Heart palpitations, thrush in the mouth and throat after long term use, headache, slight muscle shaking, mild throat discomfort, coughing, hoarseness, dry mouth, increased heart rate (heart beating fast), nausea, diarrhoea, muscle cramps, dizziness, light headedness, bad taste, thirstiness, tiredness, agitation, restlessness, nervousness, sleep disturbances, weight gain.

Pulmicort: Hoarseness, sore irritated throat, irritation of the tongue and mouth, dry mouth, thrush in the tongue and mouth after long term use, cough, mild throat discomfort, bad taste, diarrhoea, nausea, immediate and delayed mild allergic reactions (e.g. rash), severe allergic reactions, angioedema (swelling), headache, light-headedness, thirst, tiredness, weight gain.

It is important that you contact the Study Doctor to let them know if you have any new or unusual symptoms. You should not let this delay you seeking medical help if you require it.

Your Study Doctor will discuss the best way of managing any side effects with you.

Pregnancy (Female Participants only)

In general clinical practice the study inhalers may be used during pregnancy, however females pregnant, breastfeeding or planning pregnancy at the time of recruitment will be excluded from participating in the trial. This is because it is recognised that during pregnancy, asthma symptoms may change, therefore it is important that while you are pregnant your asthma control is tailored to your symptoms. Should you become pregnant during the course of the trial you should inform the Study Doctor at the earliest opportunity. They will withdraw you from the study, so that you can be placed under the care of your GP, who will prescribe you the most appropriate inhaler regimen during your pregnancy.

Female participants are requested to use effective contraception during the study.

Risks associated with blood tests

You may experience some discomfort during the taking of a blood sample and there is always the risk of bleeding, swelling and bruising at the site of the needle during sampling. All samples will be taken by trained staff.

You may hold beliefs about a sacred and shared value of all or any blood samples removed. There are a range of views held by Māori around these issues; some iwi disagree with storage of blood samples and advise their people to consult prior to participation in research where this occurs. However it is acknowledged that individuals have the right to choose.

Risks associated with spirometry tests

You may feel shortness of breath or dizziness during or after performing the breathing exercises, however this will be temporary and you will be monitored constantly throughout the tests by study staff. You will be seated at all times for the tests.

Benefits

Clinical research mainly focuses on moderate to severe asthma, however most adults with asthma have mild disease. This study will provide evidence to help guide clinical management of mild asthmatics and improve asthma guidelines. The information we get from this study may therefore help us to better treat patients with asthma in the future although we are uncertain which patients will benefit the most from each of the study regimens at this point in time.

You will be provided with asthma education and inhalers for the duration of the study and will be reimbursed $50.00 for your time and transport costs after each visit.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

We will ask you during the consent process if you would like to be informed of the results of this study. This can be e-mailed or posted to you. Please keep in mind there may be a substantial delay between taking part in the study and receiving the results due to ongoing recruitment for the study.

We will contact you with new information that becomes available to us during the study about adverse and beneficial effects related to the study which may have an impact on your health.

You may have a friend, family or whānau member to support and help you understand the risks and/or benefits of this study and any other explanation you may require.

Privacy and Confidentiality

Information will be collected from you at the study visits, including medical and personal information. We may also need to access your Hospital, Afterhours or GP clinic records to check health care information (for example to check the date you last visited your GP and whether they prescribed prednisone). We will collect your NHI number to check your hospital records for any admissions due to your asthma. The sponsor will not use your NHI number for any other purpose as part of the study.

The data we collect for the study will be coded, so that your name is removed and replaced with a unique participant identification number. Your blood samples will also be coded in the same way, to protect your privacy. No material which could personally identify you will be used in any reports on this study.

We will collect your address at Visit 1 and this will be sent to the sponsor. Your address will be used to obtain information from Statistics New Zealand about the deprivation index status of the area you live in. The sponsor will not use your address details for any other purpose as part of the study.

Data sent to the sponsor will be held in a secure database, which is only accessible to trained study and sponsor staff.

The study site staff will have access to your health information during the study and will keep a log to link your unique number to your name and other identifiable information.

The sponsor will monitor the study. The study monitor will have access to your health information to make sure that the study is being run properly.

The ethics committee and regulatory authority may also access your health records if the study is audited. This is to make sure that participants are protected and to make sure the study was run properly.

The Study Staff, sponsor and all other parties will keep your information secure and confidential, as per the law. Your health information may be given if required by law.

Original data records will be kept in a secure place for 15 years and then destroyed.

Withdrawal

You may withdraw from the study at any time, without having to give a reason. If you would like to withdraw, please inform the Study Doctor. Participation in this study may also be stopped if the Study Doctor decides it is not in your best interests to continue, or if the Study as a whole is stopped for safety reasons.

If you decide to withdraw, you can let us know verbally and you do not have to attend a withdrawal visit, however if you agree, we will ask you to attend an optional final visit in order to return the study inhalers and discuss any questions you may have. We will also ask if you wish to sign an optional withdrawal form, to confirm if we are able to use your study data up until your withdrawal.

If you choose to withdraw and your blood sample has not yet been tested, you may ask the Study Doctor to destroy it. If the result of your blood sample is known at the time you withdraw, it will be included in the study results.

If you do not attend the withdrawal visit and complete the withdrawal form, we will use the data you have provided up until the point of your withdrawal.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact the Study Doctor, Jo Hardy:

Phone: *04 805 0147*
Email: *jo.hardy@mrinz.ac.nz*

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

For Māori health support please contact:

Phone: *04 806 0948*
Email: *wcs@ccdhb.org.nz*

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

Consent Form

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

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

Participant ID:	

If you need an INTERPRETER, please tell us.

Please tick to indicate you consent to the following:

I have read, or have had read to me in a language I understand, and I understand the Participant Information Sheet.	
I have been given sufficient time to consider whether or not to participate in this study.	
I have had the opportunity to use a legal representative, whānau/ family support or a friend to help me ask questions and understand the study, if required.	
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	
I consent to the research staff collecting and processing my information, including information about my health.	
I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.	
I agree to the study monitor (or sponsor approved representative), an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.	
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.	
I understand the compensation provisions in case of injury during the study.	
I know who to contact if I have any questions about the study in general.	
I understand my responsibilities as a study participant.	
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	

I understand that my address and NHI number will be collected and sent to the study sponsor.	

I wish to receive a summary of the results from the study.	Yes ☐	No ☐

Declaration by participant:

I hereby consent to take part in this study.

Participant's name: _____

Signature: _____ Date: _____

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name: _____

Signature: _____ Date: _____

Appendix 4: Asthma Control Questionnaire-5 (ACQ-5)

The 5-item version of the ACQ questionnaire contains five questions on participants' symptoms, which are assessed on a 7-point scale from 0 (representing good control) to 6 (representing poor control). The overall score is the mean score of all questions for which responses are provided. A minimum of 4 out of 5 questions must be answered for a valid overall ACQ score. The ACQ is conducted at Visits 1 to 6 with overall score evaluated at each visit.[3]

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

(SYMPTOMS ONLY)

ENGLISH VERSION FOR NEW ZEALAND

For further information:

Elizabeth Juniper, MCSP, MSc
Professor
20 Marcuse Fields
Bosham, West Sussex
PO18 8NA, England
Telephone: +44 1243 572124
Fax: +44 1243 573680
E-mail: juniper@qoltech.co.uk
Web: http://www.qoltech.co.uk

This translation has been made possible through
a grant from GLAXOSMITHKLINE
Translated by MAPI RESEARCH INSTITUTE
Senior Translator: Ray Kirk

NOVEMBER 2001

INSTRUCTIONS

Please answer questions 1 - 5.

Please circle the number of the response that best describes how you have been during the **past week**.

1. In general, during the **past week**, how often were you **woken by your asthma** during the night?

0 Never
1 Hardly ever
2 A few times
3 Several times
4 Many times
5 A great many times
6 Unable to sleep because of asthma

2. In general, during the **past week**, how **uncomfortable were your asthma symptoms when you woke up** in the morning?

0 No symptoms
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Quite severe symptoms
5 Severe symptoms
6 Very severe symptoms

3. In general, during the **past week**, how **limited were you in your activities** because of your asthma?

0 Not limited at all
1 Very slightly limited
2 Slightly limited
3 Moderately limited
4 Very limited
5 Extremely limited
6 Totally limited

4. In general, during the **past week**, how much **shortness of breath** did you experience because of your asthma?

0 None
1 A very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

5. In general, during the **past week**, how much time did you **wheeze?**

0 Never
1 Hardly any of the time
2 A little of the time
3 A moderate amount of the time
4 A lot of the time
5 Most of the time
6 All the time

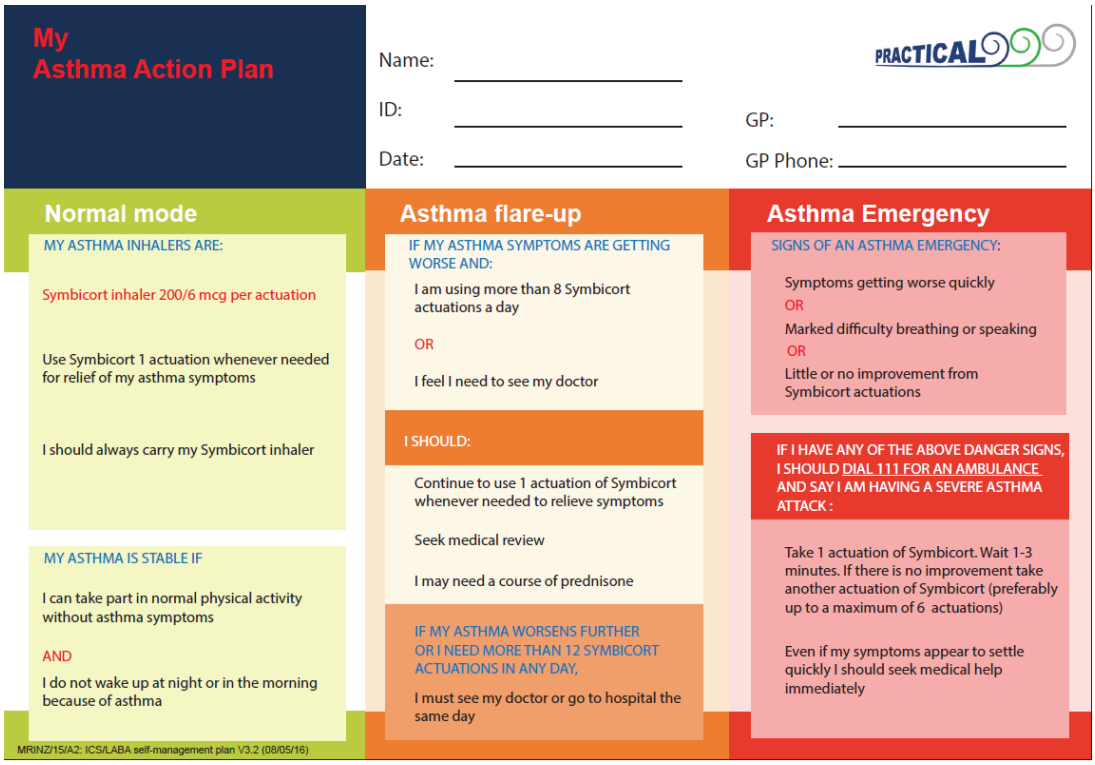
Participant signature: _____

Date Completed: ____/ _____/ _____

DD MMM YYYY

Appendix 5: Asthma management plans

Budesonide/formoterol Group Asthma Action Plan Front



My
Asthma Action Plan

Name: _____

ID: _____

Date: _____

PRACTICAL

GP: _____

GP Phone: _____

Normal mode

MY ASTHMA INHALERS ARE:

Symbicort inhaler 200/6 mcg per actuation

Use Symbicort 1 actuation whenever needed for relief of my asthma symptoms

I should always carry my Symbicort inhaler

MY ASTHMA IS STABLE IF

I can take part in normal physical activity without asthma symptoms

AND

I do not wake up at night or in the morning because of asthma

Asthma flare-up

IF MY ASTHMA SYMPTOMS ARE GETTING WORSE AND:

I am using more than 8 Symbicort actuations a day

OR

I feel I need to see my doctor

I SHOULD:

Continue to use 1 actuation of Symbicort whenever needed to relieve symptoms

Seek medical review

I may need a course of prednisone

IF MY ASTHMA WORSENS FURTHER OR I NEED MORE THAN 12 SYMBICORT ACTUATIONS IN ANY DAY,

I must see my doctor or go to hospital the same day

Asthma Emergency

SIGNS OF AN ASTHMA EMERGENCY:

Symptoms getting worse quickly

OR

Marked difficulty breathing or speaking

OR

Little or no improvement from Symbicort actuations

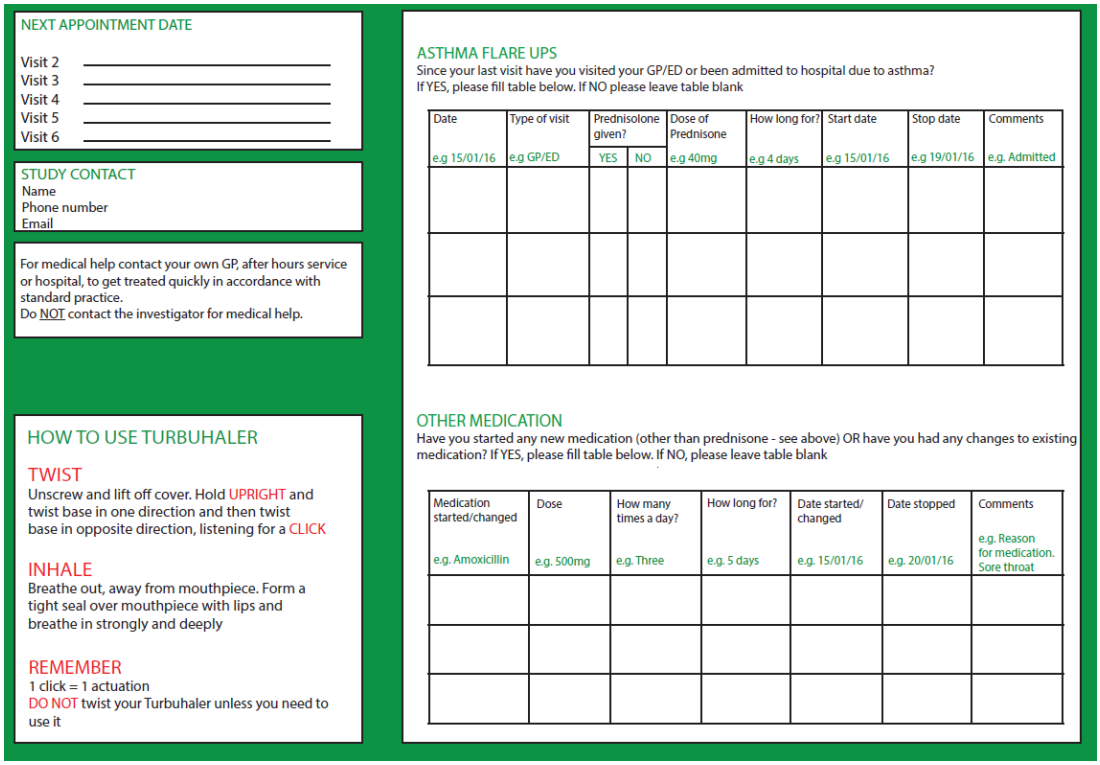
IF I HAVE ANY OF THE ABOVE DANGER SIGNS, I SHOULD DIAL 111 FOR AN AMBULANCE AND SAY I AM HAVING A SEVERE ASTHMA ATTACK :

Take 1 actuation of Symbicort. Wait 1-3 minutes. If there is no improvement take another actuation of Symbicort (preferably up to a maximum of 6 actuations)

Even if my symptoms appear to settle quickly I should seek medical help immediately

MRINZ/15/A2: ICS/LABA self-management plan V3.2 (08/05/16)

Budesonide/formoterol Group Asthma Action Plan Reverse



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

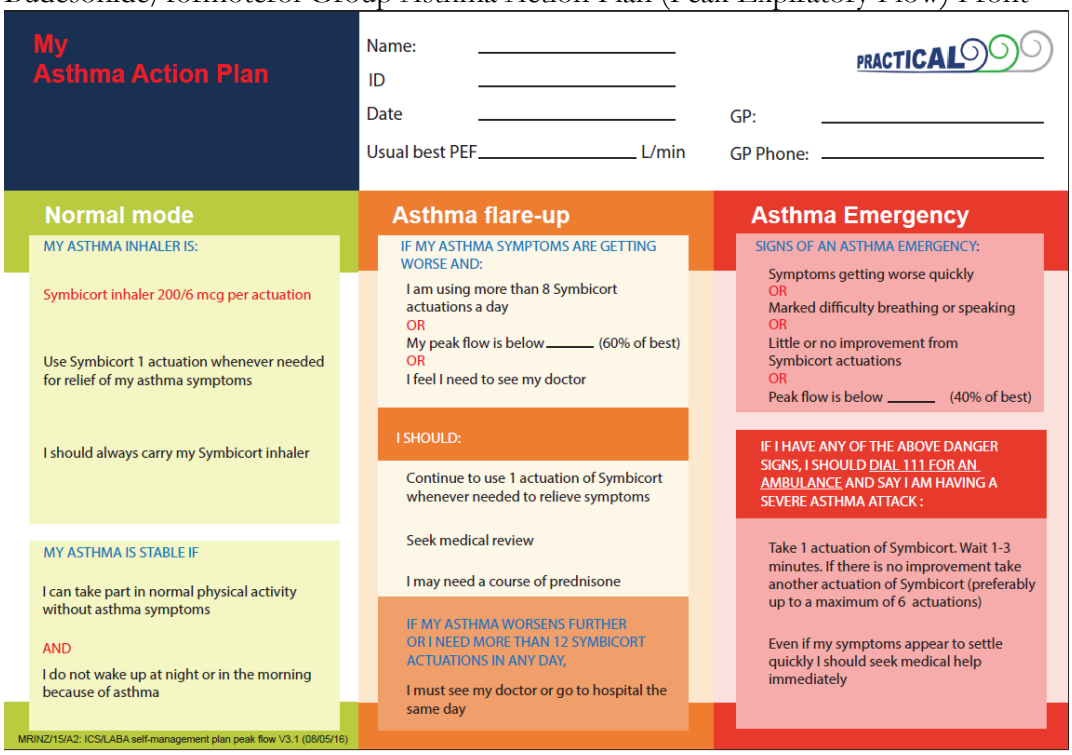
ASTHMA FLARE UPS
Since your last visit have you visited your GP/ED or been admitted to hospital due to asthma?
If YES, please fill table below. If NO please leave table blank

Date	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

Budesonide/formoterol Group Asthma Action Plan (Peak Expiratory Flow) Front



My Asthma Action Plan

Name: _____

ID _____

Date _____

Usual best PEF _____ L/min

PRACTICAL

GP: _____

GP Phone: _____

Normal mode

MY ASTHMA INHALER IS:

Symbicort inhaler 200/6 mcg per actuation

Use Symbicort 1 actuation whenever needed for relief of my asthma symptoms

I should always carry my Symbicort inhaler

MY ASTHMA IS STABLE IF

I can take part in normal physical activity without asthma symptoms

AND

I do not wake up at night or in the morning because of asthma

Asthma flare-up

IF MY ASTHMA SYMPTOMS ARE GETTING WORSE AND:

I am using more than 8 Symbicort actuations a day
OR
My peak flow is below _____ (60% of best)
OR
I feel I need to see my doctor

I SHOULD:

Continue to use 1 actuation of Symbicort whenever needed to relieve symptoms

Seek medical review

I may need a course of prednisone

IF MY ASTHMA WORSENS FURTHER OR I NEED MORE THAN 12 SYMBICORT ACTUATIONS IN ANY DAY,

I must see my doctor or go to hospital the same day

Asthma Emergency

SIGNS OF AN ASTHMA EMERGENCY:

Symptoms getting worse quickly
OR
Marked difficulty breathing or speaking
OR
Little or no improvement from Symbicort actuations
OR
Peak flow is below _____ (40% of best)

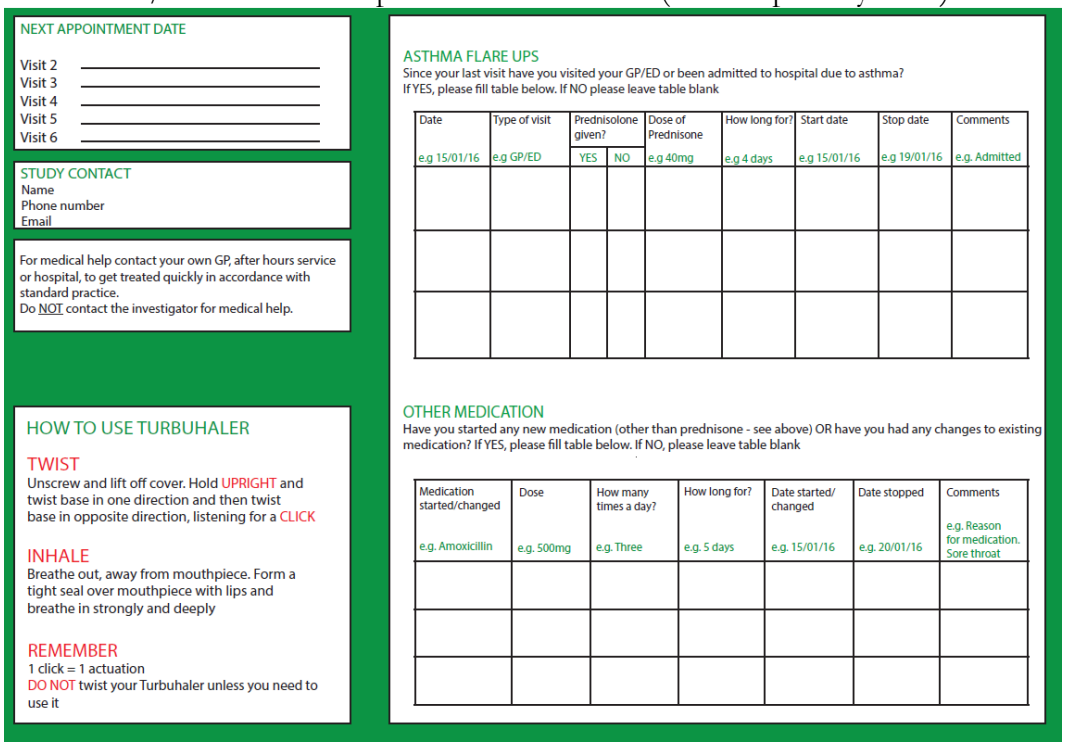
IF I HAVE ANY OF THE ABOVE DANGER SIGNS, I SHOULD DIAL 111 FOR AN AMBULANCE AND SAY I AM HAVING A SEVERE ASTHMA ATTACK :

Take 1 actuation of Symbicort. Wait 1-3 minutes. If there is no improvement take another actuation of Symbicort (preferably up to a maximum of 6 actuations)

Even if my symptoms appear to settle quickly I should seek medical help immediately

MRINZ/15/A2: ICS/LABA self-management plan peak flow V3.1 (08/05/16)

Budesonide/formoterol Group Asthma Action Plan (Peak Expiratory Flow) Reverse



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	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

Maintenance Budesonide Group Asthma Action Plan Front

My
Asthma Action Plan

Name: _____

ID: _____

Date: _____

PRACTICAL

GP: _____

GP Phone: _____

Normal mode

MY ASTHMA INHALERS ARE:

Pulmicort inhaler 200mcg per actuation

Terbutaline inhaler 250 mcg per actuation

MY REGULAR PREVENTER TREATMENT:
Take one Pulmicort actuation in the morning and one Pulmicort actuation in the evening every day

RELIEVER:
Use Terbutaline 2 actuations whenever needed for relief of my asthma symptoms

I should always carry my Terbutaline inhaler

MY ASTHMA IS STABLE IF

I can take part in normal physical activity without asthma symptoms

AND

I do not wake up at night or in the morning because of asthma

Asthma flare-up

IF MY ASTHMA SYMPTOMS ARE GETTING WORSE AND:

I am using more than 16 Terbutaline actuations a day

OR

I feel I need to see my doctor

I SHOULD:

Continue to use regular Pulmicort treatment PLUS 2 actuations of Terbutaline whenever needed to relieve symptoms

Seek medical review

I may need a course of prednisone

IF MY ASTHMA WORSENS FURTHER OR I NEED MORE THAN 24 TERBUTALINE ACTUATIONS IN ANY DAY,

I must see my doctor or go to hospital the same day

Asthma Emergency

SIGNS OF AN ASTHMA EMERGENCY:

Symptoms getting worse quickly

OR

Marked difficulty breathing or speaking

OR

Little or no improvement from Terbutaline actuations

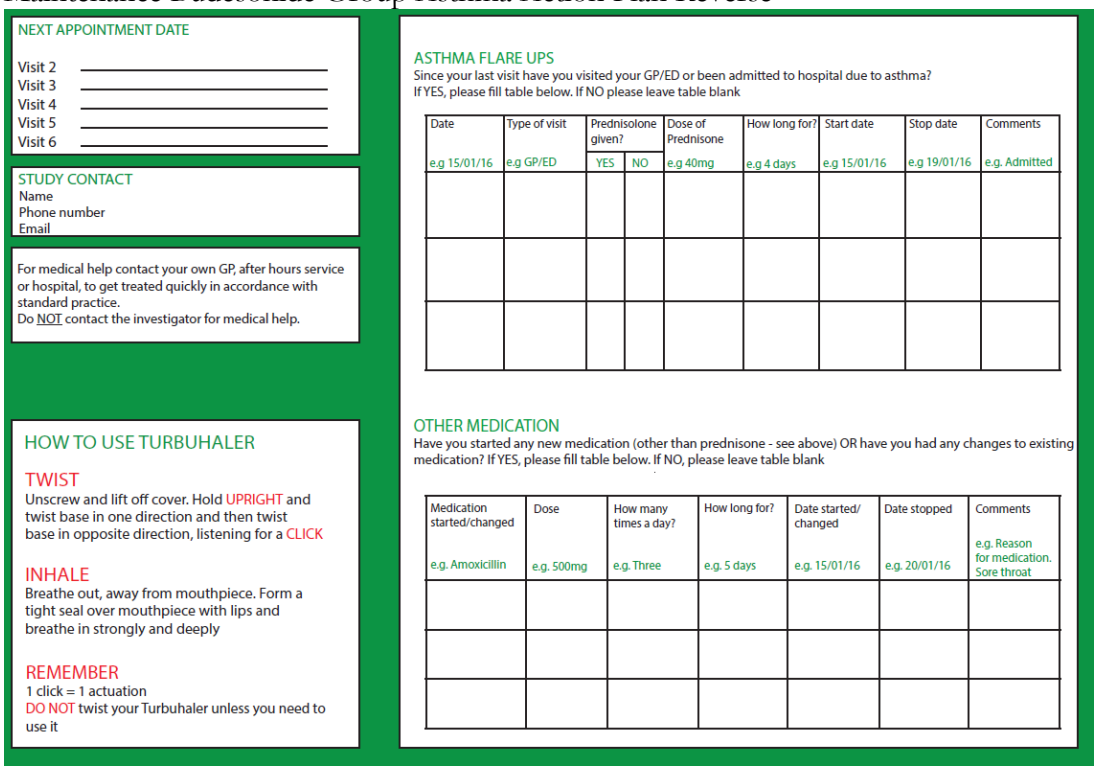
IF I HAVE ANY OF THE ABOVE DANGER SIGNS, I SHOULD DIAL 111 FOR AN AMBULANCE AND SAY I AM HAVING A SEVERE ASTHMA ATTACK:

Take 2 actuations of Terbutaline. Wait 1-3 minutes. If there is no improvement take another 2 actuations of Terbutaline (preferably up to a maximum of 12 actuations)

Even if my symptoms appear to settle quickly I should seek medical help immediately

MRINZ/15/A2: ICS/SABA self-management plan V3.2 (08/05/16)

Maintenance Budesonide Group Asthma Action Plan Reverse



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.
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HOW TO USE TURBUHALER

TWIST
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INHALE
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If YES, please fill table below. If NO please leave table blank

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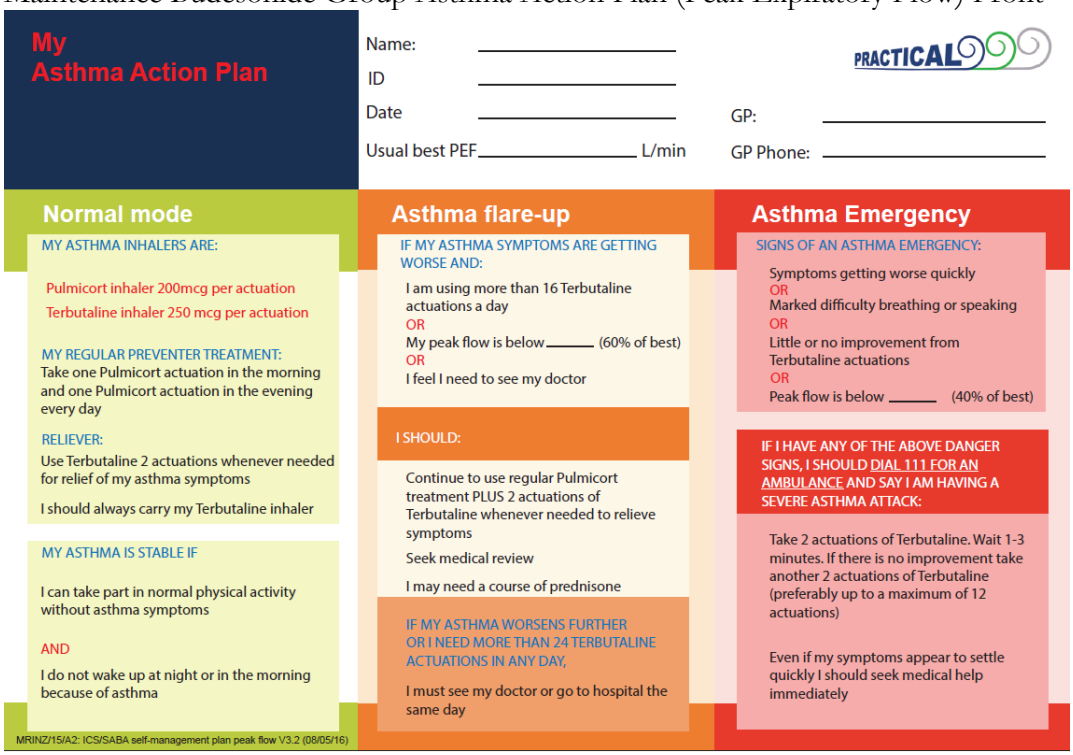
Have you started any new medication (other than prednisone - see above) OR have you had any changes to existing medication? If YES, please fill table below. If NO, please leave table blank

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

Maintenance Budesonide Group Asthma Action Plan (Peak Expiratory Flow) Front



My
Asthma Action Plan

Name: _____
ID _____
Date _____
Usual best PEF _____ L/min

PRACTICAL

GP: _____
GP Phone: _____

Normal mode

MY ASTHMA INHALERS ARE:

Pulmicort inhaler 200mcg per actuation
Terbutaline inhaler 250 mcg per actuation

MY REGULAR PREVENTER TREATMENT:
Take one Pulmicort actuation in the morning and one Pulmicort actuation in the evening every day

RELIEVER:
Use Terbutaline 2 actuations whenever needed for relief of my asthma symptoms

I should always carry my Terbutaline inhaler

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AND

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Asthma flare-up

IF MY ASTHMA SYMPTOMS ARE GETTING WORSE AND:

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OR
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Asthma Emergency

SIGNS OF AN ASTHMA EMERGENCY:

Symptoms getting worse quickly
OR
Marked difficulty breathing or speaking
OR
Little or no improvement from Terbutaline actuations
OR
Peak flow is below _____ (40% of best)

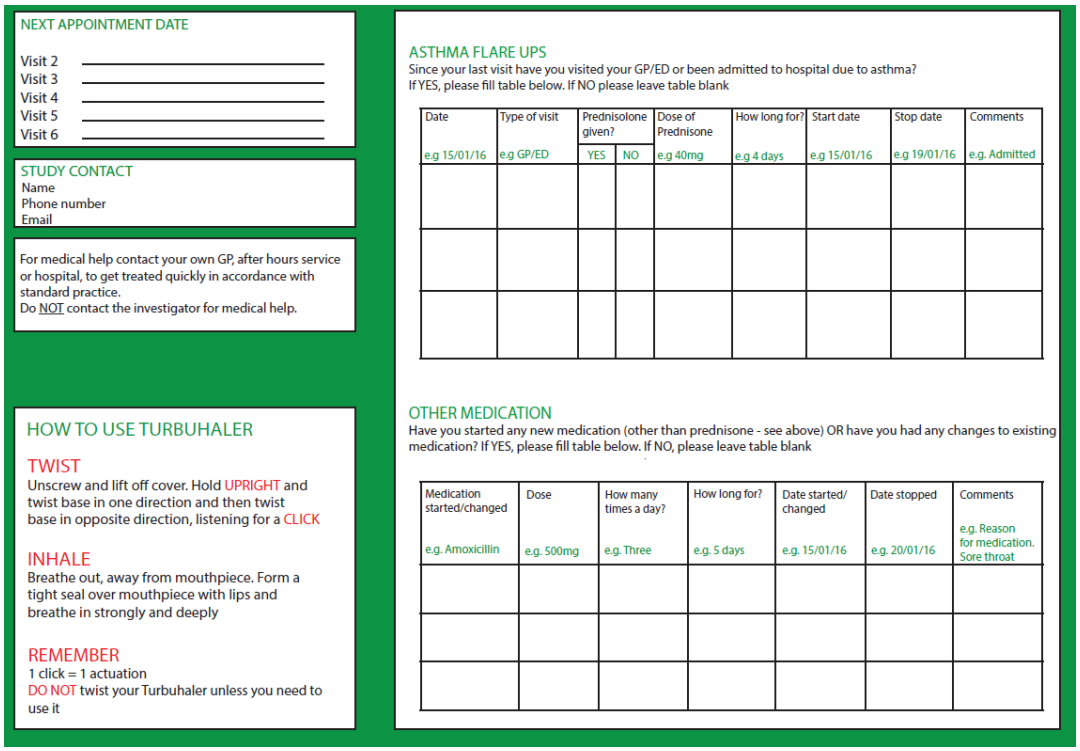
IF I HAVE ANY OF THE ABOVE DANGER SIGNS, I SHOULD DIAL 111 FOR AN AMBULANCE AND SAY I AM HAVING A SEVERE ASTHMA ATTACK:

Take 2 actuations of Terbutaline. Wait 1-3 minutes. If there is no improvement take another 2 actuations of Terbutaline (preferably up to a maximum of 12 actuations)

Even if my symptoms appear to settle quickly I should seek medical help immediately

MRINZ/15/A2: ICS/SABA self-management plan peak flow V3.2 (08/05/16)

Maintenance Budesonide Group Asthma Action Plan (Peak Expiratory Flow) Reverse



NEXT APPOINTMENT DATE

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

STUDY CONTACT
Name
Phone number
Email

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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
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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	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

Appendix 6: Method for calculating predicted normal FEV1

1. Predicted normal FEV1 values will be calculated according to Quanjer et al 2012.[14]

The equation for calculating predicted normal FEV1 is of the form:
PN FEV1 = exp(a0 + a1·ln(Height) + a2·ln(Age) + a3·AfrAm + a4·NEAsia + a5·SEAsia + a6·Other + Mspline)

The following input variables are used in the predicted normal FEV1 equation:

- Height is the patient's height in cm (to the nearest 0.1 cm, recorded at Visit 1)
- Age is the patient's age in years (to the nearest 0.1 years) – this should be recalculated based on the visit date and patient's date of birth
- AfrAm is equal to 1 if the patient's ethnic population is African American, 0 otherwise
- NEAsia is equal to 1 if the patient's ethnic population is North East Asian, 0 otherwise
- SEAsia is equal to 1 if the patient's ethnic population is South East Asian, 0 otherwise
- Other is equal to 1 if the patient's ethnic population is Other/Mixed, 0 otherwise

The constants a0, a1, a2, a3, a4 and a5 depend on the patient's sex, as outlined in the table below:

CONSTANT	MALES	FEMALES
A0	-10.3420	-9.6987
A1	2.2196	2.1211
A2	0.0574	-0.0270
A3	-0.1589	-0.1484
A4	-0.0351	-0.0149
A5	-0.0881	-0.1208
A6	-0.0708	-0.0708

The final term in the predicted normal FEV1 equation, Mspline, is obtained a lookup table based on the patient's age and sex.
For patients aged 25 or over, the following equation may be used to approximate Mspline in place of the lookup tables:
Mspline = b0 + b1·(Age/100) + b2·(Age/100)2 + b3·(Age/100)3 + b4·(Age/100)4 + b5·(Age/100)5
where b0, b1, b2, b3, b4 and b5 are constants that depend on the patient's sex, as outlined in the table below:

CONSTANT	MALES	FEMALES
B0	0.3901	0.0552
B1	-1.0579	1.6029
B2	1.4743	-6.4845
B3	-2.1077	10.2723
B4	-0.1215	-9.8630
B5	0.8873	3.8802

2. Lookup table for final term

The following lookup table is used for determining the value of Mspline in the equation for calculating predicted normal FEV1. For ages other than those listed here, the value is derived using linear interpolation of the two nearest ages (i.e. those ages either side of the patient's actual age).

The lookup table is available from the Global Lung Function Initiative website (URL at the time of writing: http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/quanjer-gli-2012-regression-equations-and-lookup-tables.aspx).

AGE	MALE	FEMALE	AGE	MALE	FEMALE	AGE	MALE	FEMALE
18	0.19237	0.17849	26.75	0.17601	0.16972	35.5	0.10782	0.13368
18.25	0.19560	0.17972	27	0.17393	0.16895	35.75	0.10592	0.13223
18.5	0.19840	0.18076	27.25	0.17184	0.16818	36	0.10401	0.13075
18.75	0.20082	0.18162	27.5	0.16975	0.16741	36.25	0.10208	0.12925
19	0.20288	0.18232	27.75	0.16766	0.16662	36.5	0.10015	0.12772
19.25	0.20462	0.18289	28	0.16558	0.16583	36.75	0.09820	0.12616
19.5	0.20605	0.18333	28.25	0.16352	0.16503	37	0.09624	0.12458
19.75	0.20719	0.18366	28.5	0.16147	0.16422	37.25	0.09428	0.12298
20	0.20807	0.18391	28.75	0.15943	0.16339	37.5	0.09230	0.12136
20.25	0.20868	0.18407	29	0.15741	0.16255	37.75	0.09032	0.11971
20.5	0.20904	0.18415	29.25	0.15541	0.16169	38	0.08833	0.11805
20.75	0.20918	0.18416	29.5	0.15342	0.16082	38.25	0.08633	0.11636
21	0.20911	0.18410	29.75	0.15144	0.15993	38.5	0.08432	0.11466
21.25	0.20886	0.18397	30	0.14946	0.15903	38.75	0.08230	0.11293
21.5	0.20844	0.18377	30.25	0.14750	0.15811	39	0.08028	0.11119
21.75	0.20787	0.18351	30.5	0.14554	0.15718	39.25	0.07825	0.10942
22	0.20715	0.18318	30.75	0.14360	0.15623	39.5	0.07621	0.10764
22.25	0.20629	0.18279	31	0.14166	0.15527	39.75	0.07416	0.10584
22.5	0.20530	0.18234	31.25	0.13973	0.15429	40	0.07210	0.10402
22.75	0.20419	0.18182	31.5	0.13781	0.15329	40.25	0.07003	0.10219
23	0.20296	0.18125	31.75	0.13589	0.15226	40.5	0.06795	0.10034
23.25	0.20162	0.18062	32	0.13399	0.15121	40.75	0.06587	0.09847
23.5	0.20018	0.17994	32.25	0.13210	0.15014	41	0.06378	0.09659
23.75	0.19865	0.17922	32.5	0.13021	0.14903	41.25	0.06168	0.09469
24	0.19704	0.17847	32.75	0.12833	0.14791	41.5	0.05958	0.09278
24.25	0.19536	0.17770	33	0.12646	0.14675	41.75	0.05747	0.09085
24.5	0.19361	0.17690	33.25	0.12460	0.14557	42	0.05536	0.08891
24.75	0.19180	0.17610	33.5	0.12274	0.14436	42.25	0.05326	0.08696
25	0.18994	0.17529	33.75	0.12089	0.14312	42.5	0.05115	0.08500
25.25	0.18804	0.17447	34	0.11904	0.14185	42.75	0.04904	0.08303
25.5	0.18610	0.17366	34.25	0.11718	0.14055	43	0.04694	0.08105
25.75	0.18413	0.17286	34.5	0.11532	0.13923	43.25	0.04484	0.07906
26	0.18213	0.17206	34.75	0.11346	0.13788	43.5	0.04274	0.07707
26.25	0.18011	0.17128	35	0.11159	0.13651	43.75	0.04065	0.07507
26.5	0.17807	0.17050	35.25	0.10971	0.13511	44	0.03855	0.07306

AGE	MALE	FEMALE
44.25	0.03647	0.07105
44.5	0.03438	0.06903
44.75	0.03230	0.06701
45	0.03022	0.06499
45.25	0.02814	0.06296
45.5	0.02606	0.06093
45.75	0.02398	0.05889
46	0.02190	0.05685
46.25	0.01981	0.05480
46.5	0.01771	0.05274
46.75	0.01562	0.05068
47	0.01351	0.04861
47.25	0.01140	0.04654
47.5	0.00928	0.04446
47.75	0.00715	0.04237
48	0.00502	0.04027
48.25	0.00287	0.03817
48.5	0.00071	0.03605
48.75	-0.00146	0.03394
49	-0.00364	0.03181
49.25	-0.00583	0.02967
49.5	-0.00804	0.02752
49.75	-0.01026	0.02536
50	-0.01250	0.02320
50.25	-0.01475	0.02102
50.5	-0.01701	0.01883
50.75	-0.01929	0.01663
51	-0.02157	0.01441
51.25	-0.02388	0.01219
51.5	-0.02619	0.00995
51.75	-0.02852	0.00770
52	-0.03087	0.00544
52.25	-0.03323	0.00316
52.5	-0.03561	0.00087
52.75	-0.03800	-0.00143
53	-0.04042	-0.00374
53.25	-0.04284	-0.00607
53.5	-0.04529	-0.00841
53.75	-0.04775	-0.01077
54	-0.05023	-0.01314
54.25	-0.05273	-0.01552
54.5	-0.05524	-0.01791
54.75	-0.05776	-0.02032
AGE	MALE	FEMALE
55	-0.06031	-0.02274
55.25	-0.06286	-0.02517
55.5	-0.06544	-0.02762
55.75	-0.06802	-0.03008
56	-0.07063	-0.03255
56.25	-0.07324	-0.03504
56.5	-0.07588	-0.03754
56.75	-0.07853	-0.04006
57	-0.08119	-0.04259
57.25	-0.08387	-0.04514
57.5	-0.08656	-0.04770
57.75	-0.08927	-0.05027
58	-0.09199	-0.05286
58.25	-0.09473	-0.05546
58.5	-0.09748	-0.05808
58.75	-0.10024	-0.06071
59	-0.10302	-0.06335
59.25	-0.10581	-0.06601
59.5	-0.10861	-0.06868
59.75	-0.11143	-0.07137
60	-0.11425	-0.07407
60.25	-0.11709	-0.07678
60.5	-0.11994	-0.07951
60.75	-0.12281	-0.08224
61	-0.12568	-0.08500
61.25	-0.12856	-0.08776
61.5	-0.13146	-0.09054
61.75	-0.13436	-0.09333
62	-0.13727	-0.09613
62.25	-0.14019	-0.09895
62.5	-0.14312	-0.10178
62.75	-0.14606	-0.10462
63	-0.14900	-0.10748
63.25	-0.15194	-0.11034
63.5	-0.15489	-0.11322
63.75	-0.15785	-0.11612
64	-0.16081	-0.11903
64.25	-0.16377	-0.12195
64.5	-0.16674	-0.12488
64.75	-0.16971	-0.12783
65	-0.17269	-0.13079
65.25	-0.17567	-0.13377
65.5	-0.17865	-0.13675
AGE	MALE	FEMALE
65.75	-0.18163	-0.13976
66	-0.18462	-0.14277
66.25	-0.18761	-0.14580
66.5	-0.19061	-0.14884
66.75	-0.19361	-0.15190
67	-0.19661	-0.15496
67.25	-0.19961	-0.15804
67.5	-0.20262	-0.16114
67.75	-0.20563	-0.16424
68	-0.20864	-0.16736
68.25	-0.21165	-0.17049
68.5	-0.21467	-0.17362
68.75	-0.21768	-0.17677
69	-0.22070	-0.17993
69.25	-0.22372	-0.18310
69.5	-0.22674	-0.18627
69.75	-0.22976	-0.18946
70	-0.23278	-0.19265
70.25	-0.23580	-0.19585
70.5	-0.23882	-0.19906
70.75	-0.24185	-0.20227
71	-0.24486	-0.20549
71.25	-0.24788	-0.20872
71.5	-0.25090	-0.21195
71.75	-0.25392	-0.21519
72	-0.25693	-0.21843
72.25	-0.25994	-0.22168
72.5	-0.26296	-0.22493
72.75	-0.26597	-0.22819
73	-0.26897	-0.23145
73.25	-0.27198	-0.23472
73.5	-0.27498	-0.23798
73.75	-0.27798	-0.24125
74	-0.28097	-0.24452
74.25	-0.28396	-0.24780
74.5	-0.28695	-0.25107
74.75	-0.28993	-0.25434
75	-0.29291	-0.25762
75.25	-0.29589	-0.26090
75.5	-0.29886	-0.26417
75.75	-0.30182	-0.26744

3. Predicted FEV1 Data Processing

The relevant demographic data from the eCRF (age, sex, height and ethnicity) will be exported into excel format and imported (according to the instructions and process outlined) into the GLI-2012 Excel Sheet Calculator Version 4, 25 May 2014 (URL at time of writing available at http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/excel-sheet-calculator.aspx).

The output from this process (FEV1 predicted) will then be imported into the final analysis dataset.

Articles

Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial

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Summary

Background In adults with mild asthma, a combination of an inhaled corticosteroid with a fast-onset long-acting β-agonist (LABA) used as reliever monotherapy reduces severe exacerbations compared with short-acting β-agonist (SABA) reliever therapy. We investigated the efficacy of combination budesonide–formoterol reliever therapy compared with maintenance budesonide plus as-needed terbutaline.

Methods We did a 52-week, open-label, parallel-group, multicentre, superiority, randomised controlled trial at 15 primary care or hospital-based clinical trials units and primary care practices in New Zealand. Participants were adults aged 18–75 years with a self-reported doctor's diagnosis of asthma who were using SABA for symptom relief with or without maintenance low to moderate doses of inhaled corticosteroids in the previous 12 weeks. We randomly assigned participants (1:1) to either reliever therapy with budesonide 200 µg–formoterol 6 µg Turbuhaler (one inhalation as needed for relief of symptoms) or maintenance budesonide 200 µg Turbuhaler (one inhalation twice daily) plus terbutaline 250 µg Turbuhaler (two inhalations as needed). Participants and investigators were not masked to group assignment; the statistician was masked for analysis of the primary outcome. Six study visits were scheduled: randomisation, and weeks 4, 16, 28, 40, and 52. The primary outcome was the number of severe exacerbations per patient per year analysed by intention to treat (severe exacerbations defined as use of systemic corticosteroids for at least 3 days because of asthma, or admission to hospital or an emergency department visit because of asthma requiring systemic corticosteroids). Safety analyses included all participants who had received at least one dose of study treatment. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12616000377437.

Findings Between May 4, 2016, and Dec 22, 2017, we assigned 890 participants to treatment and included 885 eligible participants in the analysis: 437 assigned to budesonide–formoterol as needed and 448 to budesonide maintenance plus terbutaline as needed. Severe exacerbations per patient per year were lower with as-needed budesonide–formoterol than with maintenance budesonide plus terbutaline as needed (absolute rate per patient per year 0·119 *vs* 0·172; relative rate 0·69, 95% CI 0·48–1·00; p=0·049). Nasopharyngitis was the most common adverse event in both groups, occurring in 154 (35%) of 440 patients receiving as-needed budesonide–formoterol and 144 (32%) of 448 receiving maintenance budesonide plus terbutaline as needed.

Interpretation In adults with mild to moderate asthma, budesonide–formoterol used as needed for symptom relief was more effective at preventing severe exacerbations than maintenance low-dose budesonide plus as-needed terbutaline. The findings support the 2019 Global Initiative for Asthma recommendation that inhaled corticosteroid–formoterol reliever therapy is an alternative regimen to daily low-dose inhaled corticosteroid for patients with mild asthma.

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See Online for appendix

Introduction

Most people with asthma have intermittent or mild disease. Despite generally having few symptoms, these patients still have exacerbations.[1,2] Many of these exacerbations could be prevented by low-dose inhaled corticosteroids,[2,3] but health-care professionals often do not prescribe these drugs to patients with intermittent or mild disease and such patients may be poorly adherent, as the intermittent nature of symptoms makes commitment to a regular maintenance regimen problematic.[4–6]

An alternative approach is to use a combination of an inhaled corticosteroid with formoterol (a fast-onset long-acting β-agonist [LABA]) as reliever monotherapy, which reduces the risk of severe exacerbations by more than half compared with a short-acting β-agonist (SABA) reliever alone.[7,8] However there is

Research in context

Evidence before this study

Inhaled corticosteroids taken regularly reduce exacerbation risk in patients with mild asthma; however, in clinical practice adherence to inhaled corticosteroids is poor and the burden of disease from exacerbations is substantive. An alternative approach that potentially overcomes the problem of poor adherence is the use of an inhaled corticosteroid–formoterol combination as sole reliever therapy, thereby titrating use according to symptoms. We searched MEDLINE and Embase for studies published between Jan 1, 2000, and July 1, 2019, using the terms "inhaled corticosteroid-formoterol", "budesonide-formoterol", "as-required", "asthma", "adults", and "randomised controlled trial". Four studies of adults with mild or moderate asthma were identified which investigated the efficacy of budesonide–formoterol reliever monotherapy, all of which were published after this study was designed. In two studies, comparisons were made versus short-acting β-agonist (SABA) reliever monotherapy or with maintenance budesonide plus SABA reliever therapy; in one, versus maintenance budesonide plus SABA reliever therapy; and in one versus regular budesonide-formoterol plus SABA reliever therapy. Budesonide-formoterol reliever therapy was superior to SABA reliever therapy in patients with mild asthma, reducing the risk of severe exacerbations by at least 50% after a follow-up of 12 months. Of the three studies investigating budesonide-formoterol reliever therapy and maintenance budesonide plus SABA reliever therapy in patients with mild asthma, two were regulatory and one was a real-world study; there was non-inferiority in severe exacerbation risk in the two regulatory studies, whereas the real world study reported a significantly lower severe exacerbation risk with budesonide-formoterol reliever therapy compared with maintenance budesonide therapy plus SABA reliever. Budesonide-formoterol reliever monotherapy was inferior to regular budesonide-formoterol plus as-needed SABA for the outcome of treatment failure but not different for severe exacerbations in patients with moderate asthma. As a result, there is uncertainty about the relative efficacy and safety of inhaled corticosteroid–formoterol reliever monotherapy compared with maintenance inhaled corticosteroid plus SABA reliever therapy .

Added value of this study

This was the first independently funded open-label study comparing inhaled corticosteroid–formoterol reliever therapy with maintenance inhaled corticosteroid plus SABA reliever therapy in adults with mild to moderate asthma in a real-world setting. Budesonide–formoterol reliever therapy resulted in fewer severe exacerbations, and patients on this therapy had a longer time to first severe exacerbation, compared with patients on maintenance budesonide plus as-needed terbutaline. FENO was lower with budesonide maintenance. There was no significant between-group difference in asthma symptom control as measured by Asthma Control Questionnaire 5. The findings of sub-group analyses were consistent with the treatment effect being similar in all patient subgroups, suggesting that the findings are generalisable across the spectrum of mild and moderate asthma.

Implications of all the available evidence

Budesonide–formoterol reliever therapy is superior to maintenance budesonide plus SABA reliever therapy in adults with mild to moderate asthma in the real-world setting, reducing the risk of severe exacerbations without a clinically important worsening in asthma symptom control. Together the available evidence suggests that, for prevention of severe exacerbations, budesonide–formoterol reliever therapy is preferred to SABA reliever therapy for step 1 treatment, confirming the recommendation in the Global Initiative for Asthma (GINA) 2019 guidelines that adults and adolescents with asthma should not be treated with SABA alone. The evidence also supports the inclusion of budesonide–formoterol reliever therapy as an alternative to maintenance low-dose corticosteroids plus SABA reliever in GINA step 2. With the addition of this study, the evidence now also suggests that, of these two regimens, budesonide–formoterol reliever therapy might be the preferred option for prevention of severe exacerbations in mild to moderate asthma.

uncertainty about the relative efficacy and safety of this regimen compared with maintenance inhaled corticosteroid plus as-needed SABA. Two large, randomised, placebo-controlled trials[7,9] reported non-inferiority in the risk of severe exacerbations between these two regimens, whereas an open-label study more closely aligned to clinical practice reported a halving of the risk of severe exacerbations with budesonide–formoterol reliever therapy compared with maintenance budesonide plus as-needed salbutamol.[8] In all three studies, maintenance budesonide plus as-needed SABA achieved greater improvement in symptom control, although this improvement was less than the minimum clinically important difference.

We designed the PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta agonist (PRACTICAL) study with the aim of comparing the efficacy of as needed budesonide–formoterol reliever therapy with maintenance budesonide plus as-needed terbutaline in an open-label clinical trial in adults with mild to moderate asthma. This is the first independently funded randomised controlled trial comparing inhaled corticosteroid–formoterol as sole reliever therapy with maintenance inhaled corticosteroid plus SABA reliever therapy in patients with asthma for whom low dose maintenance inhaled corticosteroid therapy was recommended at step 2 of the 2014 Global Initiative for Asthma (GINA) strategy.[10]

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Methods

Study design and participants

PRACTICAL was an investigator-led, pragmatic, 52 week, open-label, parallel-group, multicentre, superiority, randomised controlled trial undertaken at 15 primary care or hospital-based clinical trials units and primary care practices across New Zealand. Ethical approval was provided by the Northern B Health and Disability Ethics Committee. The study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and the trial protocol has been published.[11]

Eligible participants were adults aged 18 to 75 with a self-reported doctor's diagnosis of asthma who were either taking SABA reliever therapy alone or SABA reliever together with low to moderate doses of inhaled corticosteroids in the 12 weeks before randomisation. The main inclusion criteria were 1) for those who had not used an inhaled corticosteroid in the past 12 weeks, the presence of asthma symptoms or need for a SABA on at least two occasions in the past 4 weeks, or waking because of asthma at least once in the past 4 weeks, or a history of a severe asthma exacerbation requiring oral corticosteroids in the past 52 weeks, and 2) for those who had used an inhaled corticosteroid in the previous 12 weeks at low or moderate doses (≤800 µg/day budesonide equivalent), partly or well controlled asthma as defined by GINA 2014,[10] or uncontrolled asthma with poor adherence or unsatisfactory inhaler technique. Exclusion criteria were oral corticosteroid use for asthma in the 6 weeks before randomisation, representing recent unstable asthma; a home supply of oral corticosteroids used as part of an asthma action plan; self-reported use of LABA, leukotriene receptor antagonists, theophylline, anticholinergic drugs, or cromones in the 12 weeks before randomisation; self-reported admission to an intensive care unit for asthma ever; a self-reported diagnosis of chronic obstructive pulmonary disease, bronchiectasis, or interstitial lung disease; self-reported greater than 20 pack-years smoking history, or the onset of respiratory symptoms after the age of 40 in current or ex-smokers with at least 10 pack-years smoking history; pregnancy or planned pregnancy during the study period; unwilling or unable to switch from current asthma treatment regimen; other illnesses that were likely to compromise participant safety or affect the feasibility of results, at the discretion of the investigator. There was no standardised method of pre-screening across sites. All participants provided written informed consent.

Randomisation and masking

We randomly assigned participants (1:1) to either reliever therapy with budesonide–formoterol or maintenance budesonide plus terbutaline as needed. Randomisation was stratified by recruitment site and inhaled corticosteroid use before enrolment, using a computer-generated sequence with a block size of eight per site, generated by the statistician. The allocation sequence was concealed by the electronic case report form system until after randomisation. Site investigators enrolled participants. Participants and investigators were not masked to group assignment; the statistician was masked for analysis of the primary outcome variable.

Procedures

Participants in the budesonide–formoterol group received budesonide 200 µg–formoterol 6 µg (Symbicort Turbuhaler, AstraZeneca), one inhalation for relief of symptoms as required. Patients in the maintenance budesonide plus terbutaline as needed group received budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca), one inhalation twice daily plus terbutaline 250 µg (Bricanyl Turbuhaler, AstraZeneca), two inhalations for relief of symptoms as required. Participants were provided with an asthma action plan that included when to seek medical review for worsening asthma and a log for recording urgent medical visits and systemic corticosteroid use (appendix pp 27–30). Electronic inhaler usage monitors (Adherium, Auckland, New Zealand) that recorded the date and time of inhaler actuations[12] were incorporated in all inhalers dispensed to a subgroup of participants at two study sites. Participants were aware that the electronic monitors recorded the date and time of their inhaler use. The data from the electronic monitors were not viewed or analysed during the study and participants were made explicitly aware of this. All participants remained under the care of their usual health-care practitioners throughout the study.

Six study visits were scheduled over 52 weeks at week 0 (randomisation visit), and weeks 4, 16, 28, 40, and 52. Baseline participant characteristics were collected at the randomisation visit. On-treatment forced expiratory volume in one s (FEV_1)[13] and fractional exhaled nitric oxide (FENO) were measured at weeks 0, 16, and 52. Peripheral blood eosinophils were measured at baseline, as was serum periostin in a subgroup. The five-question version of the Asthma Control Questionnaire (ACQ-5)[14] was completed at every study visit. At all study visits following randomisation participants were asked if they had needed to seek urgent medical care for asthma or used oral corticosteroids for worsening asthma. Participants self-reported all adverse or serious adverse events at their subsequent follow up visits. Inhaler technique was checked at every study visit and participants were reminded of their study asthma plan. The schedule of investigations and assessments is in the protocol.[11] Patients were withdrawn in the event of treatment failure, defined as either an increase in asthma treatment for 14 days or more made by a health-care provider because of unstable asthma, or uncontrolled asthma resulting in safety concerns as judged by the investigator.

Outcomes

The primary outcome was the number of severe asthma exacerbations per patient per year. Severe asthma

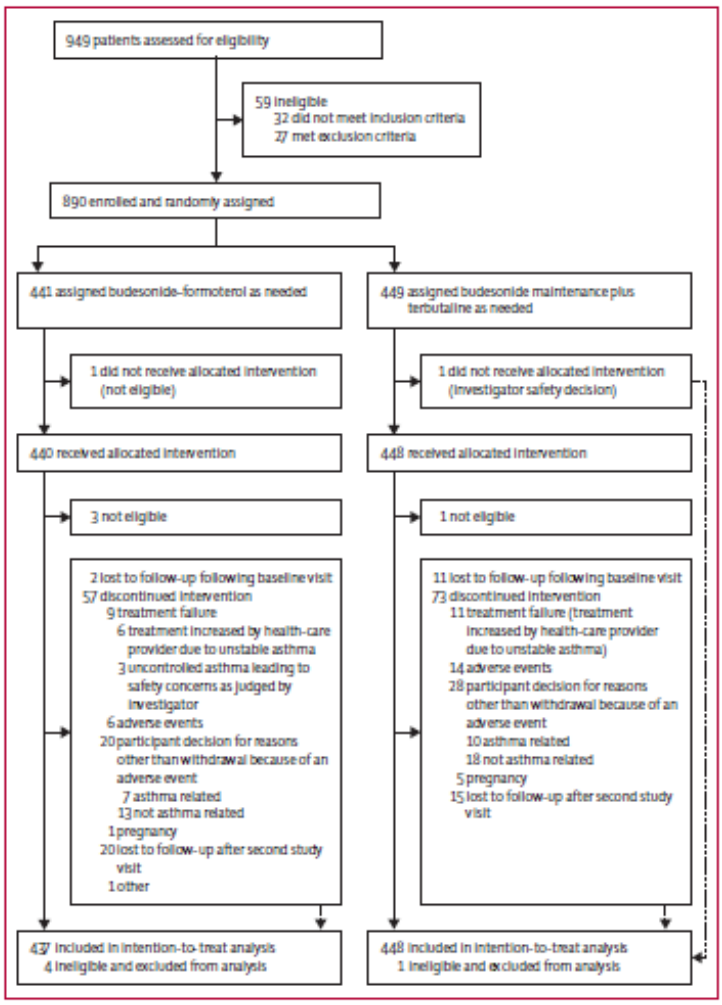


Figure 1: Trial profile

exacerbations were defined by American Thoracic Society/European Respiratory Society (ATS/ERS) criteria:[13] the use of systemic corticosteroids for at least 3 days because of asthma, or hospital admission or emergency department visit because of asthma, requiring systemic corticosteroids.

Secondary outcomes were the proportion of severe exacerbations defined by the same criteria as for the primary outcome; the proportion of patients with a least one severe exacerbation; time to first severe exacerbation; number of asthma exacerbations per patient per year, including both moderate and severe exacerbations, defined as worsening asthma resulting in unplanned medical review (primary care, visit to emergency department, or hospital admission) or worsening asthma resulting in use of systemic corticosteroids for any duration; time to first moderate or severe exacerbation; the proportion of patients withdrawn due to treatment failure; proportion of participants prescribed oral corticosteroids for at least three days following urgent medical review; the ACQ-5 score (the mean of five questions about asthma symptoms during the previous week, each scored on a 7-point scale between 0 [no impairment] and 6 [maximum impairment]);[14] on-treatment FEV_1 (L),[13] FENO (parts per billion); adverse events and serious adverse events; and for the electronic monitoring substudy, electronically-recorded budesonide dose per day and electronically-recorded β-agonist actuations per day. Full details of the methods and the statistical analysis plan are in the online protocol[11] and appendix (pp 7–11).

Statistical analysis

A sample size of 445 in each treatment arm, which accounted for a 10% dropout rate, had a 90% power and α 5%, to detect a relative rate of severe exacerbations of 0·62, representing a reduction from 0·30 to 0·185 per patient per year. A masked re-estimation of the sample size was done at a planned interim safety analysis after 500 participants had been recruited and randomly assigned to treatment. The overall rate of severe exacerbations at the interim analysis was 0·09 across both arms, lower than the estimated 0·30 per patient per year. The required sample size for the study to be adequately powered to detect the proposed 0·62 relative rate of severe exacerbations would have been 2112 participants. Neither the funding nor the capacity was in place to allow this and therefore the study continued with the original primary outcome variable and planned sample size of 890.

For the electronic monitoring substudy, a sample size of 55 in each treatment arm, which accounted for a 10% dropout rate, had 90% power and α 5% to detect an 18% difference in mean daily budesonide use (μg/day) with budesonide–formoterol, compared with 264 μg/day in the maintenance budesonide plus as-needed terbutaline group. This calculation was based on data from our previous study of inhaled corticosteroid adherence in stable asthma in which participants took a mean (SD) 66% (27) of their prescribed inhaled corticosteroid dose.[15]

The statistical analysis was an intention-to-treat superiority analysis. The primary analysis was comparison of the number of severe exacerbations per patient per year by Poisson regression with an offset for the time of observation. No adjustment for over-dispersion was used because the degree of freedom was close to the deviance indicating that over-dispersion was unlikely to be a problem. A sensitivity analysis was undertaken to account for different distributions of potential predictors of response, and modelled the following covariates: age, sex, ethnicity, smoking status, baseline ACQ-5, severe exacerbation in previous year (yes/no), baseline inhaled

corticosteroid use, baseline SABA use (in previous 4 weeks), baseline FENO, and baseline blood eosinophil count. Analysis of the combined rate of moderate and severe exacerbations per patient per year was likewise by Poisson regression with an offset for number of days in the study.

Survival analysis with Kaplan-Meier plots and Cox proportional hazards regression was used to calculate the hazard ratio (HR) for the time to first severe exacerbation and first moderate or severe exacerbation. Continuous variables, such as ACQ-5 and FEV_1, were compared by *t* tests and mixed linear models to examine patterns of change with time. For FENO, data were log transformed and differences in logarithms analysed as the ratio of geometric means. Interaction models were used to test for subgroup effects. The Wilcoxon test and the Hodges-Lehmann estimate of location difference were used to compare oral corticosteroid doses between treatment groups. Logistic regression was used to compare the proportion of participants with at least one severe exacerbation, the proportion of participants who withdrew, adverse events, and severe adverse events between the two treatment arms. The safety analysis dataset included all participants who had received at least one dose of randomised treatment. Summary statistics were presented as the number (%) for categorical data and mean (SD) or median (IQR) for continuous data. The primary analysis of the electronic monitoring substudy was comparison of mean budesonide dose per day by *t* test. SAS version 9.4 was used for all analyses. An independent data safety monitoring committee reviewed all serious adverse events. This trial was registered with the Australian and New Zealand Clinical Trials Registry, ACTRN12616000377437.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 4, 2016, and Dec 22, 2017, we assigned 890 participants to treatment (figure 1); the intention-to-treat dataset included 885 eligible participants (baseline characteristics are in table 1, and the appendix pp 31–34). No follow-up data were available for 14 participants (appendix p 35). At study entry participants had a mean ACQ-score of 1·15; 12% reported a severe exacerbation in the previous 12 months. At baseline 264 (30%) of 885 participants were taking SABA reliever therapy alone and 621 (70%) were taking an inhaled corticosteroid. The results of all statistical analyses undertaken are in the appendix (pp 13–25 and 37–62).

The rate of severe asthma exacerbations was lower with as-needed budesonide–formoterol than budesonide

	Budesonide-formoterol as needed (n=437)	Budesonide maintenance plus terbutaline as needed (n=448)
Age (years)	43·3 (15·2)	42·8 (16·7)
BMI (kg/m²)	29·4 (7·1)	28·0 (5·8)
Sex		
Female	244 (56%)	241 (54%)
Male	193 (44%)	207 (46%)
Ethnic origin		
Asian	29 (7%)	34 (8%)
European	342 (78%)	357 (80%)
Māori	41 (10%)	31 (7%)
Pacific	20 (5%)	16 (4%)
Other	5 (1%)	10 (2%)
Smoking status		
Current	39 (9%)	24 (5%)
Ex-smoker	123 (28%)	112 (25%)
Never	275 (63%)	312 (70%)
Pack-years (among ever smokers)	4·5 (4·7)	4·6 (4·7)
Age at diagnosis (years)	19·5 (17·7)	18·8 (18·1)
Patient-reported use of inhaled corticosteroids in the 12 weeks before enrolment	305 (70%)	316 (71%)
Patient-reported adherence to inhaled corticosteroids in the 4 weeks before enrolment (percentage of prescribed dose)	54·8% (37·0; n=304)	58·6% (47·3; n=315)
Patient-reported use of inhaled corticosteroids ever	390 (89%)	381 (85%)
Patient-reported SABA use in 4 weeks before enrolment (occasions per week)		
Mean (SD)	4·3 (6·0)	4·9 (7·5)
Median (IQR)	2·0 (1·0–5·5)	2·3 (1·0–6·0)
Range	0–70	0–84
Hospital admissions for asthma during lifetime (number per patient)	0·7 (5·1)	0·5 (2·1)
Severe exacerbation in the previous 12 months		
0	384 (88%)	396 (88%)
1	45 (10%)	41 (9%)
2	5 (1%)	7 (2%)
3	3 (<1%)	3 (<1%)
4	0	1 (<1%)
Any	53 (12%)	52 (12%)
ACQ-5 score*	1·1 (0·8)	1·2 (0·8)
GINA symptom control		
Well controlled	101 (23%)	103 (23%)
Partly controlled	209 (48%)	226 (51%)
Uncontrolled	127 (29%)	119 (27%)
On-treatment FEV_1 (percentage of predicted value†)	87·8% (16·4)	87·4% (16·3)
FENO (parts per billion)	26·0 (15·0–51·0)	30·0 (18·0–62·5)
Blood eosinophil count ($\times 10^9$ per L)	0·3 (0·2)	0·3 (0·2)

Data are means (SD) or median (IQR) unless stated otherwise. BMI=body-mass index. SABA=short-acting β_2-agonist. ACQ-5=Asthma Control Questionnaire-5. GINA=Global Initiative for Asthma. FEV_1=forced expiratory volume in 1 s. FENO=fraction of exhaled nitric oxide. *The ACQ-5 consists of five questions that assess asthma symptoms in the previous week, each of which is scored on a 7-point scale that ranges from 0 (no impairment) to 6 (maximum impairment) and averaged; a 0·5-unit change represents the minimal clinically important difference. †Participants received no specific instruction to withhold use of their bronchodilator before measurement of FEV_1.[20]

Table 1: **Baseline characteristics of intention-to-treat population**

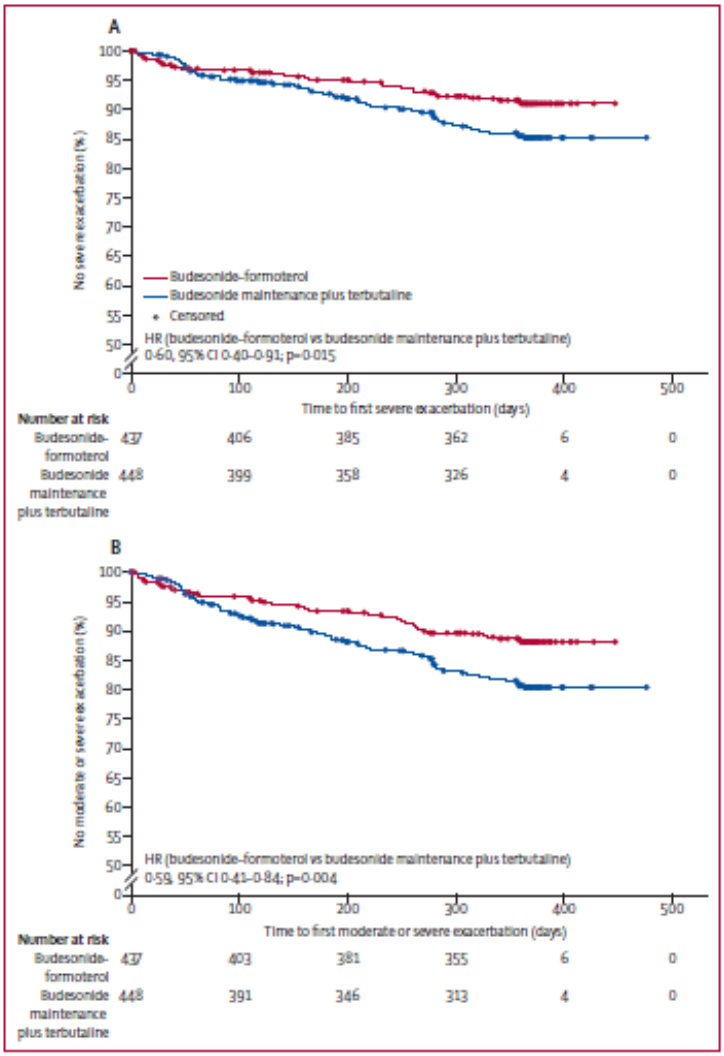


Figure 2: **Estimates of the occurrence of exacerbations in a time-to-event analysis**
Graphs show (A) time to first severe exacerbation and (B) time to first moderate or severe exacerbation. HR=hazard ratio.

maintenance plus as-needed terbutaline therapy (absolute rate per patient per year 0·119 *vs* 0·172; relative rate 0·69; 95% CI 0·48–1·00; p=0·049; appendix p 38). In the sensitivity analyses, the relative rates were robust to the included covariates (appendix p 55).

Time to first severe exacerbation was longer with budesonide–formoterol than budesonide maintenance plus as-needed terbutaline (figure 2; appendix p 39). The number of severe exacerbations resulting in an emergency department visit or hospital admission was five and 0, respectively, with as-needed budesonide-formoterol and seven and two, respectively, with budesonide maintenance plus as-needed terbutaline.

The combined moderate and severe asthma exacerbation rate was lower with as-needed budesonide–formoterol than budesonide maintenance plus as-needed terbutaline (absolute rate per patient per year 0·165 *vs* 0·237; relative rate 0·70; 95% CI 0·51–0·95; p=0·024; appendix p 41). Time to first moderate or severe exacerbation was longer with as-needed budesonide–formoterol than budesonide maintenance (figure 2; appendix p 41). The number of patients who were withdrawn because of treatment failure did not differ between groups (nine in the budesonide–formoterol group *vs* 11 in the budesonide maintenance plus terbutaline group; relative risk [RR] 0·84, 95% CI 0·35–2·00, p=0·69; appendix p 51).

Across all timepoints, ACQ-5 score with budesonide–formoterol did not differ from budesonide maintenance plus terbutaline (mean difference 0·06, 95% CI −0·005 to 0·12; p=0.07; appendix pp 15, 16, and 45). Additionally across all timepoints, FEV_1 with budesonide–formoterol did not differ from budesonide maintenance plus terbutaline (mean difference 0·006 L; 95% CI −0·026 to 0·04; p=0·69; appendix pp 17, 18, and 46).

FENO was widely skewed at baseline (table 1; appendix p 19). At 12 months, median FENO was 26 parts per billion (IQR 16–45) with budesonide–formoterol and 25 parts per billion (16–40) with budesonide maintenance plus terbutaline (appendix p 46). The geometric mean FENO across all timepoints with budesonide-formoterol was higher than with budesonide maintenance (ratio of geometric means 1·13, 95% CI 1·07–1·21; p<0·001; appendix p 47).

In participants taking SABA monotherapy at baseline, the median FENO was 32·5 parts per billion (IQR 15·0–61·5) at baseline and 24·0 parts per billion (16·0–41·0) at the final study visit in the budesonide–formoterol group versus 45·0 parts per billion (IQR 23·0–91·5) at baseline and 27 parts per billion (16–43) at the final visit in the budesonide maintenance plus terbutaline group (appendix p 48). In participants taking inhaled corticosteroids at baseline, median FENO was 25 parts per billion (IQR 15–48) at baseline and 27 parts per billion (17–46) at final study visit in the budesonide–formoterol group versus 27·5 (IQR 16·5–54·0) at baseline and 24 parts per billion (15–39) at the final visit in the budesonide maintenance group (appendix p 48).

Pre-specified analyses testing the interaction of randomised treatment with various subgroups identified that the highest quartile of baseline blood eosinophils (≥0·4×10^9/L) was associated with a greater reduction in ACQ-5, but not in severe exacerbations, with budesonide maintenance compared with as-needed budesonide–formoterol. Otherwise there was no evidence of effect modification with respect to severe exacerbations or ACQ-5, based on baseline subgroups of age, sex, ethnicity, smoking status, exacerbation history, inhaled corticosteroid use at baseline, adherence to inhaled

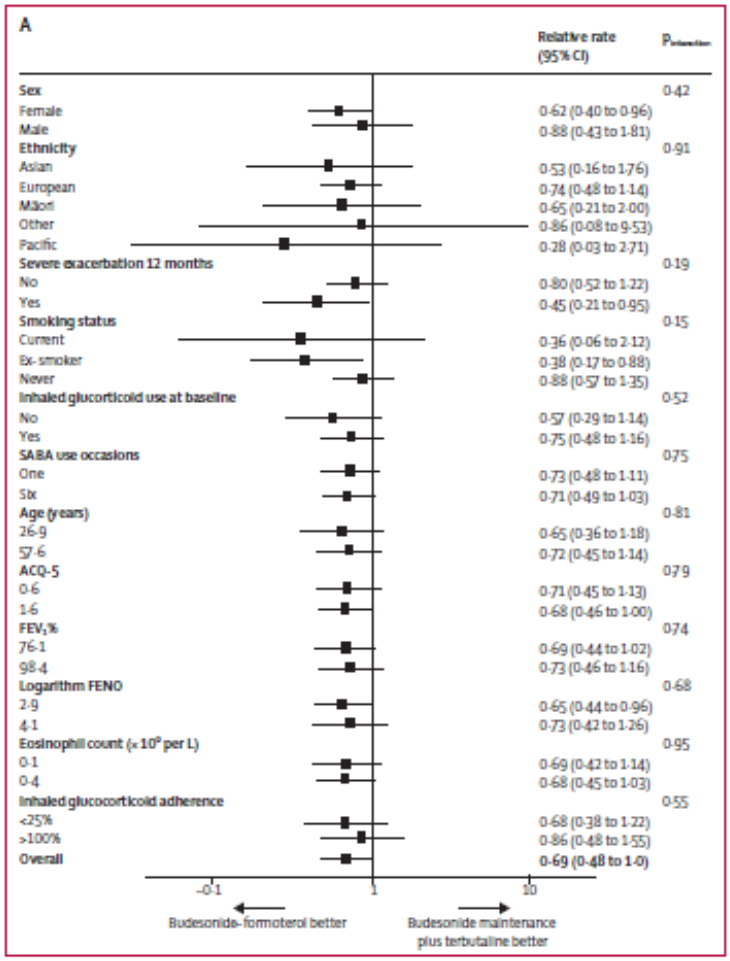
corticosteroid at baseline, baseline SABA use, ACQ-5, percentage of predicted FEV_1, and FENO (figure 3; appendix pp 56–59).

The proportion of participants prescribed oral steroids for at least 3 days following urgent medical review was 52 (78%) of 67 with as-needed budesonide–formoterol and 68 (72%) of 94 with budesonide maintenance plus terbutaline (appendix pp 39 and 42). 110 participants received inhalers containing electronic usage monitors. The characteristics of these 110 participants were similar to those of the full study population (appendix p 36). The mean dose of budesonide was less with budesonide–formoterol than with budesonide maintenance plus terbutaline, (difference −126·5 µg per day; 95% CI −171·0 to −81·9; p<0·001; table 2). Overall mean adherence with twice-daily maintenance budesonide in this subgroup was 76%.

Data on all adverse events and serious adverse events are in the appendix (pp 60–62). Nasopharyngitis was the most common adverse event in both groups, occurring in 154 (35%) of 440 patients receiving as-needed budesonide–formoterol and 144 (32%) of 448 receiving maintenance budesonide plus terbutaline (appendix p 61). The number of participants with at least one adverse event was 385 (88%) in the budesonide–formoterol group and 371 (83%) in the budesonide–maintenance plus terbutaline group. There were two hospital admissions due to asthma in the budesonide maintenance group. There were no deaths in the study.

Discussion

This randomised controlled trial provided modest evidence that combination budesonide–formoterol used as-needed for symptom relief reduced the rate of severe exacerbations compared with maintenance low-dose budesonide plus terbutaline as needed in adults with mild to moderate asthma, for whom low-dose inhaled corticosteroids or as-needed inhaled corticosteroids–formoterol are, as of 2019, recommended.[16] The 31% reduction in severe exacerbation risk was achieved despite participants using about 60% of the dose of budesonide and with no difference in symptom control. These findings suggest that titrating the dose of inhaled corticosteroids through as-needed use of a combination inhaler which also delivers a fast-onset LABA is more effective for prevention of severe exacerbations than maintenance inhaled corticosteroids with as-needed SABA in patients with mild to moderate asthma. The timing of inhaled corticosteroid administration is probably a more important determinant of efficacy than the total dose, and a symptom-driven increase in the dose of inhaled corticosteroid in worsening asthma might lead to resolution of an exacerbation before it becomes severe enough for the patient to seek medical review. The co-administration of LABA rather than SABA reliever therapy would also contribute to a reduction in severe exacerbation risk in worsening asthma.[17]



(Figure 3 continues on next page)

This study complements the findings of our Novel START study,[8] which was also undertaken in a real-world setting, enrolled patients with mild asthma taking SABA-only reliever therapy, and in which severe exacerbations was a secondary outcome measure. By contrast, in addition to enrolling patients on a SABA alone, this trial also enrolled those on maintenance low to moderate dose inhaled corticosteroids. In this study, the relative rate of severe exacerbations was 31% lower with as-needed budesonide–formoterol compared with maintenance budesonide plus as-needed terbutaline, whereas in the Novel START study,[8] the number of severe exacerbations was 56% lower with as-needed budesonide-formoterol than with maintenance budesonide plus as-needed salbutamol. In both this study and Novel START, the 95% CIs were wide with p values close to 0·05, thereby providing modest evidence of superiority, although together providing more certainty

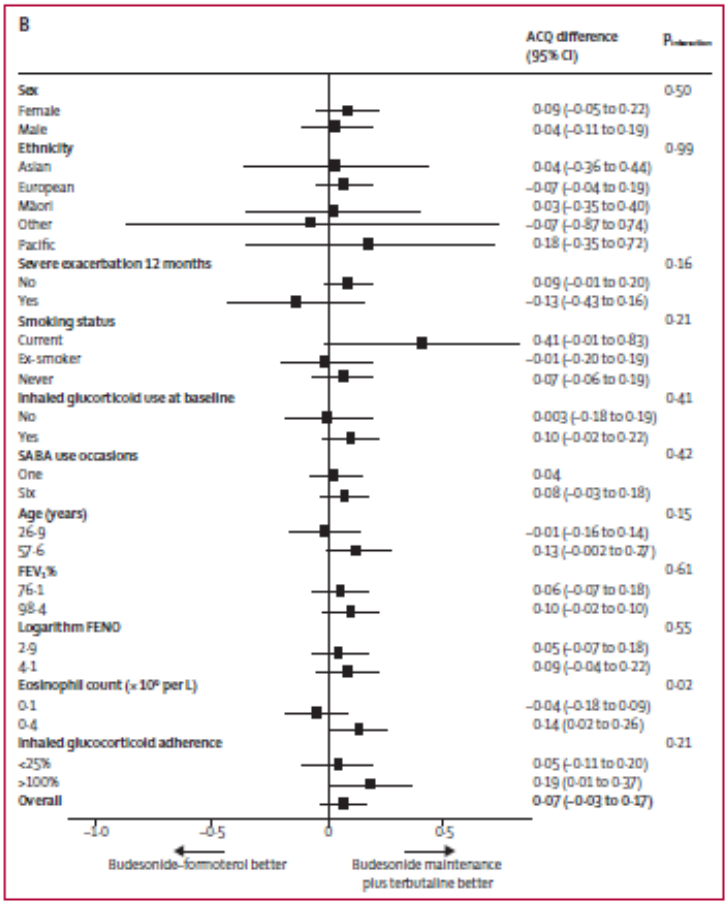


Figure 3: **Differential effect of treatment on severe exacerbations and ACQ-5 outcomes**
Data shown by potential effect-modifying baseline variables for (A) the relative rate of severe exacerbation and (B) the difference in ACQ-5 score at study end. ACQ-5=Asthma Control Questionnaire-5. SABA=short-acting β-agonist. FEV_1=forced expiratory volume in 1 s. FENO=fraction of exhaled nitric oxide.

	Budesonide-formoterol as needed (n=55)	Budesonide maintenance plus terbutaline as needed (n=55)
Inhaled corticosteroid use		
Number of budesonide-containing actuations per day		
Mean (SD)	0·9 (0·7)	1·5 (0·4)
Median (IQR)	0·8 (0·4–1·3)	1·6 (1·2–1·8)
Range†	0·0–3·4	0·1–2·3
Daily budesonide dose (μg)		
Mean (SD)	176·0 (143·0)	302·5 (84·8)
Median (IQR)	164·3 (74·0–251·7)	328·3 (245·8–364)
Range‡	6·7–682·5	26·8–458·1
β_2-agonist use		
Number of β_2-agonist-containing actuations per day		
Mean (SD)	0·9 (0·7)	0·5 (0·6)
Median (IQR)	0·8 (0·4–1·3)	0·3 (0·1–0·6)
Range†	0·0–3·4	0·0–2·7

*Use of inhaled corticosteroids and β_2-agonists was determined with electronic monitoring of the trial inhalers in a subset of 110 participants. †Range refers to the minimum and maximum mean number of actuations per day. ‡Range refers to the minimum and maximum mean daily dose.

Table 2: **Medication outcomes in electronic monitoring subgroups***

about the relative benefit of as-needed inhaled corticosteroids–formoterol in real world settings.

These findings also complement the regulatory SYGMA[7,9] studies in which there was no significant difference in risk of severe exacerbations between budesonide–formoterol reliever therapy and maintenance budesonide plus SABA reliever, with risk ratios of 0·83 and 0·97. Together, the findings from the four studies suggest that the use of budesonide-formoterol, when taken as sole reliever therapy in a comparatively real-world setting, reduces the risk of severe exacerbations compared with maintenance budesonide plus SABA reliever, whereas this benefit might not be seen in a rigidly-controlled setting with the artificial construct of regular use of a double-dummy placebo inhaler.

Our findings were consistent with those from randomised controlled trials comparing inhaled corticosteroid–formoterol reliever with SABA reliever in adults with moderate to severe asthma taking maintenance inhaled corticosteroid–LABA therapy. A meta-analysis[18] reported that in adults taking maintenance inhaled corticosteroid–LABA, the use of inhaled corticosteroid-formoterol as the reliever reduced the risk of asthma exacerbations compared with SABA reliever therapy with a relative risk of 0·68 (95% CI 0·58–0·80). This finding suggests that the magnitude of the benefit of inhaled corticosteroid–formoterol reliever therapy compared with SABA reliever therapy is similar across the spectrum of asthma severity, regardless of baseline maintenance therapy.

Our findings also complement the randomised controlled trial which reported that combination beclomethasone-salbutamol reliever therapy had similar efficacy to maintenance beclomethasone plus salbutamol reliever therapy in reducing exacerbation risk and was superior to salbutamol reliever therapy.[19]

The findings of the subgroup analyses were consistent with the treatment effect being similar in all participant subgroups, suggesting that the findings are generalisable across the spectrum of mild to moderate asthma. Although the greatest absolute benefit will probably be obtained in those with the greatest morbidity, this finding suggests that clinical profiling is not required for treatment decisions in this population. The only exception to this suggestion might be for patients with high blood eosinophil counts, in whom the highest quartile had a significant reduction in ACQ with maintenance budesonide versus as-needed budesonide-formoterol compared with the lowest quartile, although the difference

of 0·18 was less than the minimum clinically important difference of 0·5,[14] and there was no significant difference in severe exacerbations. For clinical practice, therefore, as part of shared decision making, factors such as patient preference and the likelihood of poor adherence with maintenance inhaled corticosteroid (which would expose the patient to the exacerbation risks of SABA-only treatment) could be considered in making a choice between as-needed budesonide-formoterol and daily maintenance inhaled corticosteroid plus as-needed SABA.

An intrinsic feature of budesonide–formoterol reliever therapy is that if patients are instructed to use this treatment as-needed to relieve symptoms, measures of symptom control would be expected to be worse than with maintenance inhaled corticosteroid treatment. This was noted in three previous studies, which reported higher ACQ scores with as-needed budesonide-formoterol compared with maintenance budesonide, although the differences of 0·11 to 0·15 were short of the minimum clinically important difference of 0·5.[7–9] In this study, there was no difference in ACQ-5, with the upper bound of the 95% CI being less than a quarter of the minimum clinically important difference for the ACQ-5 score, and most participants had well controlled asthma (ACQ-5 <1)[20] at study end. This finding suggests that, although adequate symptom control is an inherent concern with budesonide–formoterol reliever therapy, it is of doubtful clinical significance. Future studies will need to assess whether budesonide–formoterol reliever therapy taken prophylactically before provoking situations such as exercise, as well as as-needed for symptom relief, results in a greater level of asthma control. In this and the Novel START study, participants were neither encouraged nor discouraged from taking their reliever inhaler prior to exercise.

Consistent with findings from a previous study,[8] median FENO decreased from 32·5 parts per billion to 24 parts per billion with as-needed budesonide–formoterol in patients who were steroid-naive at baseline, confirming airways anti-inflammatory effect as measured by FENO. However, overall, maintenance budesonide plus terbutaline had a greater anti-inflammatory effect with a ratio of geometric means of FENO of 1·13, equivalent to a median FENO difference of about 5 parts per billion. The clinical significance of these FENO differences is uncertain because the ATS guidelines propose that a change of at least 20% and 10 parts per billion is required to indicate a clinically significant decrease in FENO following intervention.[21]

Limitations of our study included the open-label design; however, this is the only design that allows the real-world advantage of the inhaled corticosteroid–formoterol reliever regimen, ie, the use of a single inhaler with no maintenance treatment, to be studied. Without a requirement for a twice-daily placebo inhaler, both patient selection and behaviour were likely to be closer to that seen in usual clinical practice (PRECIS-2 wheel, appendix p 26). Study visits (after 1 month and then every 3 months) were more frequent than usual clinical practice. The study's inclusion criteria ensured that the findings are generalisable to a broad population of adults treated for mild to moderate asthma in the community.[12] Importantly, participants were not required to show bronchodilator reversibility, which has poor sensitivity and specificity for asthma.[22] Additionally, current and ex-smokers were included unless they had a greater than 20 pack-year history or for those with a 10 or more pack-year history, the onset of respiratory symptoms after the age of 40 years.

Severe exacerbation rate was the primary outcome variable, as defined and recommended by the ATS/ERS.[13] Although participants' usual health-care providers were aware of the randomised treatment when consulted during an exacerbation, there was no evidence of systematic bias. In the setting of an unplanned medical review, the probability of a participant being prescribed oral corticosteroids for at least 3 days was similar, regardless of treatment group.

The relative risk for severe exacerbation rate had wide CIs with an upper limit of 1·0. Secondary endpoints were not adjusted for multiplicity of analyses and should not be used to infer definitive treatment effects. The greater number of participants who discontinued intervention in the budesonide maintenance group might have favoured this group, as they might have had more exacerbations following withdrawal, but without having consent for follow-up or recording their treatment after withdrawal, it was not possible to determine the magnitude of any such potential bias.

Electronic monitors were attached to the randomised inhalers for only 110 participants, and as a result measures of inhaled corticosteroid and β-agonist exposure could only be derived from this subgroup. The high adherence rate of 76% in the electronic monitoring sub-group was unexpected and might relate to participants being aware that their devices recorded their inhaler use. However, it also suggests that the comparative benefit of as-needed budesonide–formoterol might have been even greater if adherence was as low as in normal clinical practice.

Our study supports one of the key recommendations of a *Lancet* asthma commission,[23] that in patients with asthma, as-required SABAs should be replaced with combination inhaled corticosteroid–fast-acting β-agonist as reliever therapy for episodic respiratory symptoms regardless of diagnostic label. The findings also provide further evidence in support of the GINA 2019 update, which recommends against SABA-only treatment of adults and adolescents with asthma, and instead recommends inhaled corticosteroid-formoterol reliever therapy for patients with mild asthma. The findings also suggest that, in community patients, as-needed inhaled corticosteroid–formoterol might be preferred over maintenance low-dose inhaled corticosteroid plus as-needed SABA.[16,24] The next priority will be to investigate the efficacy of as-needed budesonide–formoterol as sole reliever therapy in children, as well as alternative inhaled

corticosteroid–formoterol products and combination inhaled corticosteroid–SABA combinations across the spectrum of asthma severity in children and adults.

In conclusion, budesonide-formoterol reliever therapy was more effective at preventing severe exacerbations than maintenance low-dose twice-daily budesonide plus as-needed terbutaline in adults with mild to moderate asthma, with similar symptom control and a lower dose of inhaled corticosteroid.

Contributors

RB, HKR, RJH, MHa, AC, MWi, PS, JF, and MWe conceived the idea and designed the study. JH, CB, AC, JS, DH, DS, SM, AV, MWi, and JF collected the data. JM and MHo monitored the study. JH, CB, JF, HKR, RJH, JM, MHa, MWi, PS, MHo, MWe, and RB undertook data management and data analysis or data interpretation, or both. All authors had full access to the data analysis report. JH and RB wrote the first draft of the manuscript, and all authors contributed to the final version.

Declaration of interests

JH reports personal fees from AstraZeneca. CB reports personal fees from AstraZeneca and Novartis. AC reports grants from AstraZeneca, resTORbio, Regeneron, Esperion, Connect Biopharma, and Luitpold; and personal fees from AstraZeneca and GlaxoSmithKline. JF reports grants from AstraZeneca, GlaxoSmithkline, and Genentech; and personal fees and non-financial support from AstraZeneca and Boehringer Ingleheim. RJH reports grants from AstraZeneca and Boehringer Ingelheim; and personal fees from Menarini. HKR reports grants from AstraZeneca and Novartis; personal fees from AstraZeneca, GlaxoSmithKline, Merck, Novartis, Teva, Mundipharma, and Boehringer Ingelheim; and is chair of the Global Initiative for Asthma scientific committee. RB reports grants from Genentech, AstraZeneca, GlaxoSmithKline; and personal fees from AstraZeneca and Theravance. All other authors declare no competing interests.

Data sharing

De-identified individual participant data collected during the PRACTICAL trial will be shared at 2 years after article publication with no end date. These data will be available to researchers who provide a methodologically sound proposal for the purposes of achieving specific aims outlined in that proposal. Proposals should be directed to Prof Richard Beasley via email (richard.beasley@mrinz.ac.nz) and will be reviewed by the PRACTICAL study management committee. Requests to access data to undertake hypothesis-driven research will not be unreasonably withheld. To gain access, data requesters will need to sign a data access agreement and to confirm that data will only be used for the agreed purpose for which access was granted.

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