Investigation of two treatment regimens in adults with mild asthma

By

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Abstract

Introduction

In adults with mild-moderate asthma, poor adherence to daily maintenance inhaled corticosteroids (ICS) leads to increased asthma symptoms and risk of asthma exacerbations. There is evidence that symptom-driven use of a combination ICS plus a fast-onset long-acting beta$_2$-agonist (LABA) inhaler taken as needed may be an alternative to daily maintenance ICS plus as-needed short-acting beta$_2$-agonists (SABA). Through four studies: The PRACTICAL study (a randomised controlled trial) and three sub-studies nested within it, this thesis aims to investigate the efficacy of as-needed ICS-formoterol (a fast-onset LABA), exposure to and patterns of ICS and beta$_2$-agonist use, and patient preferences for and priorities concerning their asthma management.

Methods

The PRACTICAL study was a 52 week, open label, parallel group, multicentre, superiority, randomised controlled trial conducted at 15 sites throughout New Zealand. Adults aged 18-75 with a diagnosis of asthma who were taking SABA for symptom relief with or without low dose maintenance ICS were recruited. Participants were randomised 1:1 to either as-needed budesonide-formoterol (200/6mcg) one actuation for symptom relief or budesonide (200mcg) one actuation twice a day plus as-needed terbutaline (250mcg) two actuations for symptom relief. A sub-group of 110 participants had electronic inhaler monitors attached to their study inhalers which captured the time and date of every inhaler actuation. At their final study visit a total of 407 participants were eligible to complete a survey on their treatment preferences and experiences of their study randomised treatment, and a discrete choice experiment to determine their priorities for attributes of asthma management including; treatment regimen, shortness of breath, steroid dose and likelihood of an asthma flare-up.

Results

The PRACTICAL study found the rate of severe exacerbations per patient per year was lower in participants randomised to as-needed budesonide-formoterol than participants randomised to maintenance budesonide (absolute rate per patient per year 0.119 vs 0.172; relative rate 0.69; 95%CI 0.48-1.00; p=0.049).

Within the electronic monitoring sub-study, exposure to ICS was significantly lower in the group randomised to as-needed budesonide-formoterol with a mean daily ICS dose of 176.0mcg versus 302.5mcg in those randomised to maintenance budesonide (difference -126.5mcg per day; 95%CI -171.0 to -81.9; p<0.001). Use of as-needed budesonide-formoterol was associated with extended periods of no ICS use (median 156 days vs 22 days respectively) and more days where ≥4, 6 or 8 actuations of ICS were taken than maintenance budesonide.

Participants' preference for either as-needed or maintenance treatment was strongly associated with randomised treatment; 90% randomised to as-needed budesonide-formoterol preferred their randomised treatment compared to 60% of those randomised to maintenance budesonide, odds ratio for association between randomised treatment and preference was 13.3 (95%CI 7.1 to 24.7; p<0.001).

The DCE found that amount of shortness of breath was the most important attribute of asthma treatment to all participants. However, the relative importance of other attributes, particularly type of treatment regimen, varied depending on whether the participants had previously stated a preference for as-needed or maintenance treatment.

Discussion

In adults with mild-moderate asthma, as-needed budesonide-formoterol is more effective at preventing severe asthma exacerbations than maintenance budesonide at a significantly lower exposure to ICS, despite long periods of no ICS use. This suggests that timing of ICS dose and titrating it in response to symptoms is more important than total dose. If participants have experienced as-needed budesonide-formoterol,

they prefer it over maintenance budesonide suggesting this new approach to asthma treatment will be acceptable to patients. Control of shortness of breath was the most important attribute of asthma treatment to all patients. However, participants who preferred as-needed treatment were more willing to trade-off likelihood of an asthma flare up and steroid dose for their preferred treatment regimen. Knowledge of patient preferences and priorities for treatment, together with knowledge of regimen characteristics can be used in discussion with patients to determine the most appropriate regimen for them.

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Finally, I would like to thank my supervisors. Thank you to Anne La Flamme for her support and expert review; to James Fingleton for suggesting I consider doing a PhD in Wellington in the first place, and your patience and endless enthusiasm; and to Richard Beasley – thank you for the opportunity to do this PhD, I have learnt so much from you and greatly enjoyed my time at MRINZ working with you.

Personal contribution

Due to its nature, the PRACTICAL study was many years in development before I began the work for this thesis. Prof Richard Beasley was responsible for the original concept and study design. The running of the PRACTICAL study was a collaborative effort but I am particularly grateful to Jo Hardy who took primary responsibility for setting up the study and has also presented the PRACTICAL study in her thesis. I joined the study after 10 months and worked with Jo Hardy as joint principle investigators until the final six months when I took primary responsibility for the day-to day running of the study. Following completion of the study I was responsible for the closeout, data monitoring and data cleaning and contributed to writing the statistical analysis plan, interpreting the data and writing the study manuscript.

I took primary responsibility for all aspects of the electronic monitors sub-study. I took on sole responsibility for preparing and managing the electronic inhaler monitors. I recruited the majority of the participants and conducted almost every follow up visit. I wrote the statistical analysis plan for the electronic inhaler monitors, wrote the first draft of the manuscript for the sub-study and re-drafted it after comments from co-authors.

The preferences survey and discrete choice experiment were conceived, designed and implemented during the course of the PRACTICAL study in response to feedback and comments from study participants.

I took primary responsibility for the preferences survey. I designed, pilot tested, implemented, collected much of the data, wrote the statistical analysis plan and wrote the first draft of the manuscript for the preferences survey and re-drafted it after comments from co-authors.

I took primary responsibility for the discrete choice experiment. I designed, pilot tested, implemented, collected much of the data, wrote the statistical analysis plan and wrote the first draft of the manuscript for the discrete choice experiment and re-drafted it after comments from co-authors.

Publications

The following manuscripts directly relating to this thesis have been published or are in print:

i. Fingleton F, Hardy J, **Baggott C** 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 Respiratory Research (2017); 4: e000217. doi:10.1136/bmjresp-2017-000217. *I was a co-author and assisted in reviewing the manuscript*

ii. Hardy J, **Baggott C**, Fingleton J et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild-moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. The Lancet (2019); 394(10202): 919-928. doi:10.1016/S0140-6736(19)31948-8. *I was a co-primary author, I helped re-write and revised the manuscript extensively, wrote the rebuttal document, and completed the manuscript proofs prior to publication*

iii. **Baggott C**, Reddel HK, Hardy J et al. Patient preferences for symptom-driven or regular preventer treatment in mild-moderate asthma – findings from the PRACTICAL study, a randomised clinical trial. European Respiratory Journal (2020);55(4):1902073. doi: 10.1183/13993003.02073-2019. *I was the first author, I wrote the first draft, co-ordinated the co-authors, edited and prepared the manuscript for submission, and wrote the rebuttal and resubmission*.

iv. **Baggott C**, Hardy J, Sparks J et al. Titrating use of inhaled corticosteroids and beta-agonist to symptoms in mild asthma – a pre-specified analysis from the PRACTICAL study, a randomised controlled trial. Article in press, accepted by the European Respiratory Journal (2020) doi:10.1183/13993003.00170-2020. *I was the first author, I wrote the first draft, co-ordinated the co-authors, edited and prepared the manuscript for submission, and wrote the rebuttal and resubmission*.

v. **Baggott C**, Hansen P, Hancox RJ et al. What attributes do patients prefer most when choosing treatment for mild-moderate asthma? Results from a discrete choice experiment. *Thorax*. Published Online First: 27 July 2020. doi: 10.1136/thoraxjnl-2019-214343. *I was the first author, I wrote the first draft, co-ordinated the co-authors, edited and prepared the manuscript for submission, and wrote the rebuttal and resubmission*.

The following have been posters or oral presentations at conferences:

i. Hardy J, **Baggott C**, Fingleton J et al. Late Breaking Abstract - Open-label trial of budesonide/formoterol reliever therapy in mild asthma. European Respiratory Journal 2019 54: Suppl. 63, OA5332; DOI: 10.1183/13993003.congress-2019.OA5332.

ii. **Baggott C**, Hardy J, Reddel H et al. What do patients want? Preferences for two asthma regimens in mild/moderate asthma. European Respiratory Journal 2019 54: Suppl. 63, PA4188; DOI: 10.1183/13993003.congress-2019.PA4188.

iii. **Baggott C**, Hardy J, Reddel H et al. Discrete choice experiments identifying attributes influencing treatment preference in mild asthma. European Respiratory Journal 2019 54: Suppl. 63, PA4189; DOI: 10.1183/13993003.congress-2019.PA4189.

List of abbreviations used

95%CI	95% confidence interval
ACQ-5	Asthma Control Questionnaire-5
ATS	American Thoracic Society
BMQ	Beliefs about Medicines Questionnaire
BTS	British Thoracic Society
CONSORT	Consolidated Standards Of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
DCE	Discrete Choice Experiment
ERS	European Respiratory Society
FDA	Food and Drink Administration
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
GINA	Global Initiative for Asthma
GP	General Practitioner
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin E
IL	Interleukin
LOESS	Locally weighted scatterplot smoothing
IQR	Interquartile Range
LABA	Long-Acting $Beta_2$-Agonist
mcg	micrograms

Novel START	Novel Symbicort Turbuhaler Asthma Reliever Therapy
OCS	Oral Corticosteroids
PAPRIKA	Potentially All Pairwise RanKings of all possible Alternatives
PEFR	Peak Expiratory Flow Rate
ppb	parts per billion
PRACTICAL	PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta-agonist
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
SABA	Short-Acting $Beta_2$-Agonist
SD	Standard Deviation
SMART	Single Maintenance And Reliever Therapy
SYGMA	SYmbicort Given as Needed in Mild Asthma
Th1	T-helper cell 1
Th2	T-helper cell 2
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

Thesis aim

Symptom-driven budesonide-formoterol has been identified as a potential novel treatment regimen in mild-moderate asthma. This thesis has the following four aims:

1. To compare the efficacy and safety of symptom-driven budesonide-formoterol versus twice daily maintenance budesonide plus terbutaline as needed in adults with mild-moderate asthma.
2. To explore exposure to inhaled corticosteroids (ICS) and beta$_2$-agonist and patterns of use in patients taking symptom-driven budesonide-formoterol or twice daily maintenance budesonide plus terbutaline as needed.
3. To determine if patients have a preference for symptom-driven or maintenance ICS.
4. To quantify the strength of patient preferences for different aspects of asthma treatment.

Thesis outline

This thesis will have the following structure:

Chapter 1: The Introduction – this chapter will introduce and describe asthma and its management current at the time of planning of this thesis. I will explain why there is a problem with management in mild-moderate asthma, why symptom-driven budesonide-formoterol is a potential alternative regimen and the evidence for this. I will outline the clinical relevance of exposure to ICS and beta$_2$-agonists, patterns of inhaler use, and how they can be determined. The final sections of the Introduction will discuss patient preferences for asthma treatment, why they are important and how asthma treatment preference can be quantified.

Chapter 2: The PeRsonalised Asthma Combination Therapy: with Inhaled Corticosteroid And fast-onset Long-acting beta-agonist (the PRACTICAL) Study – this chapter reports a randomised controlled trial comparing the efficacy and safety of symptom-driven budesonide-formoterol with maintenance budesonide plus terbutaline as needed, and addresses my first aim.

Chapter 3: The Electronic Monitoring Sub-study – this chapter presents reports a sub-study within the PRACTICAL study where 110 participants had electronic inhaler monitors attached to their study inhalers and addresses my second aim.

Chapter 4: The Preferences Survey – this chapter reports the preferences survey nested within the PRACTICAL study which explored participants' preferences for symptom-driven and maintenance regimens. It addresses my third aim.

Chapter 5: Discrete Choice Experiment – this chapter reports the discrete choice experiment on participants' preferences and priorities for asthma treatment in relation to symptom-driven and maintenance regimens and addresses my fourth aim.

Chapter 6: Conclusion – this chapter presents the conclusions I have drawn from this thesis.

1. Introduction

1.1. Background of asthma

This first section will define asthma, the burden of disease and underlying pathophysiology. This will form a basis for understanding how inhaled therapies for asthma work, why mild-moderate asthma is undertreated, why it requires a new approach to treatment and why symptom-driven budesonide-formoterol has been identified as a potential alternative.

1.1.1. Definition of asthma

Asthma was first documented by the ancient Greeks in the Iliad, and meant "short drawn breath". However, it was Hippocrates who first used the term in a medical context[1]. Asthma is characterised by variable airflow obstruction due to bronchoconstriction particularly affecting the small airways, airway inflammation, airway hypersensitivity, and increased mucus production. This leads to symptoms of wheezing, breathlessness, chest tightness and coughing. The Global Initiative for Asthma (GINA) defines asthma as:

> "A heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation"[2].

1.1.2. Burden of disease

Asthma is the 15th most common chronic disease worldwide, with a global prevalence of 4.85% between 1990-2010[3]. Global patterns of prevalence vary, and New Zealand has one of the highest rates of asthma worldwide[4]. In 2015 the prevalence of asthma among children in New Zealand was 15.1% and 11% in adults[5], and was higher among Māori, with 20.7% of children and 14.4% of adults affected. The economic burden of asthma in New Zealand has been estimated as approximately $825NZD million per

year and it is the highest ranked disease in terms of years lost to disability in males and third highest in females[6].

Asthma exacerbations lead to a significant increase in symptom burden, healthcare utilisations, hospitalisation, and on rare occasions to death. A population based study from the United Kingdom (UK) and United States of America (USA) of 211,807 and 222,817 patients with asthma respectively, found over a year 8.4% and 12.5% of patients had one or more exacerbations[7]. In New Zealand rates of hospitalisation for asthma from 2012-2015 were 170 per 100,000 people per year with a clear correlation between lower socio-economic status and higher hospitalisation rates[5]. In 2013 there were 70 deaths from asthma in New Zealand from with highest mortality rates in people over the age of 65, and Māori and Pacific people[5]. The 2014 National Review of Asthma Deaths[8] conducted in the UK identified 195 people who died from asthma in the preceding year. Only 34% had been seen in a specialist asthma clinic in the year preceding their death, suggesting that many of them would not have been categorised as having severe asthma. While mortality from asthma declined significantly during the 1980s, in the last decade international trends in asthma mortality appear to have stalled at 0.19 deaths per 100,000[9].

Between 50-75% of people with asthma are classed as having mild disease[10]. Asthma in New Zealand affects a considerable proportion of the population, has an important impact on morbidity and has a substantial economic impact through time off work and burden on health services. Therefore, mild asthma is an important public health issue for New Zealand, and many people would have the potential to benefit from improved treatment. This provides the rationale for the work of this thesis.

1.1.3. Pathophysiology of asthma

Knowledge of the pathophysiology of asthma is necessary to understand how the two most common classes of drugs used in asthma (corticosteroids and beta-agonists) work and the rationale for using them to treat asthma.

Asthma is a heterogeneous disease caused by complicated and only partially understood interactions between genetic and environmental factors. Asthma

classically starts in childhood when it is most often associated with T helper 2 (Th2) cell driven inflammation and immunoglobulin E (IgE) mediated sensitisation to allergens in the environment such as pollen or house dust mite[11]. However, asthma can emerge later in life when it is known as adult onset asthma. In this scenario it is less likely to occur in conjunction with allergy or Type 2 inflammation. Figure 1 illustrates some of the causal pathways and subtypes of asthma which are emerging in Th2 and non-Th2 mediated asthma[12]. Asthma subtypes have been differentiated using clinical characteristics, age of onset, evidence of Type 2 inflammation, presence of eosinophilia or neutrophilia within the airways, exacerbations, evidence of airway obstruction and reversibility, and triggers. The purpose of identifying different subtypes of asthma is to recognise who will benefit from which treatments and to have a system to detect patients who are more likely to exacerbate or have a worse prognosis[13].

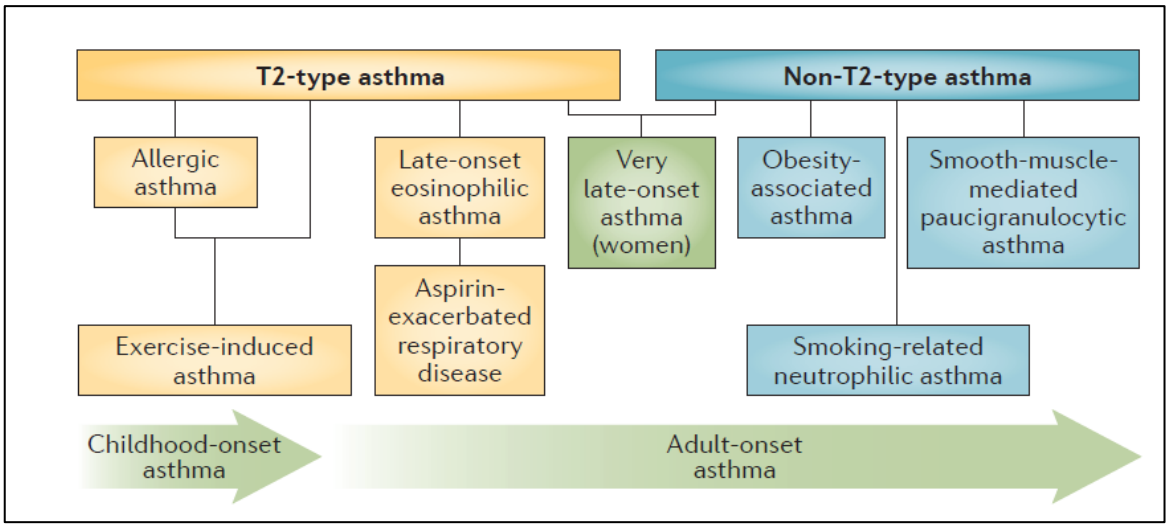

Figure 1: Asthma subtypes in Th2 and non Th2 asthma[12]

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Airway inflammation is commonplace in asthma. The T cells within the airways regulate the inflammatory cell profile and are associated with different asthma phenotypes. For example, Th2 CD4+ lymphocytes are associated with allergy driven asthma and Type 2 inflammation whereas T-helper 1 (Th1) cells are more commonly associated with neutrophilic asthma[12]. In allergic asthma, Type 2 inflammation

predominates. Th2 lymphocytes are activated by antigen-presenting airway dendritic cells, pro-allergic cytokines, eosinophils, and mast cell infiltration of the airways with an IgE mediated response to the presence of allergens. The activated Th2 lymphocytes produce further pro-allergic cytokines such as interleukin (IL)-5, IL-9, IL-13 and granulocyte-macrophage colony stimulating factor, which leads to the IgE, mast cell and eosinophilic response that characterises the condition[14]. Once sensitised to an allergen, further exposure leads initially to bronchoconstriction driven by IgE dependent release of histamine, prostaglandins and leukotrienes followed by infiltration of and activation of eosinophils and other leukocytes leading to further production of pro-allergic cytokines.

The failure to downregulate the inflammatory response and inappropriate resolution of inflammation leads to the chronic persistent airways inflammation which is present in asthma[12]. Figure 2 outlines the molecular and cellular pathways that are associated with Type 2 and eosinophilic inflammation in asthma[15]. Th2 asthma is associated with younger age of onset, presence of atopy and allergies, aspirin sensitivity, increased risk of exacerbations and exercise induced asthma[16]. Type 2 airways inflammation is one of the most important clinical features as patients with Type 2 inflammation are at greater risk of asthma exacerbations[17] and presence of Type 2 inflammation is an important predictor of treatment response. Type 2 inflammation is suppressed in most patients by corticosteroids, which is why ICS have been the mainstay of treatment for asthma since the 1980s. There is a proportion of patients with severe asthma and Type 2 inflammation which is not controlled by corticosteroids for whom there is now a selection of monoclonal antibodies targeting the Type 2 inflammatory pathway[13]. Unfortunately, the molecular mechanisms responsible for asthma in the absence of Type 2 inflammation are not well characterised and lack of effective controller medications is a significant problem.

In addition to being one of the most prevalent traits in asthma, Type 2 inflammation is also one of the most easily measurable and quantifiable. There are several different biomarkers of Type 2 inflammation in asthma; fractional exhaled nitric oxide (FeNO),

serum IgE, and blood and sputum eosinophil count. High FeNO, blood and sputum eosinophils are associated with response to corticosteroids[13].

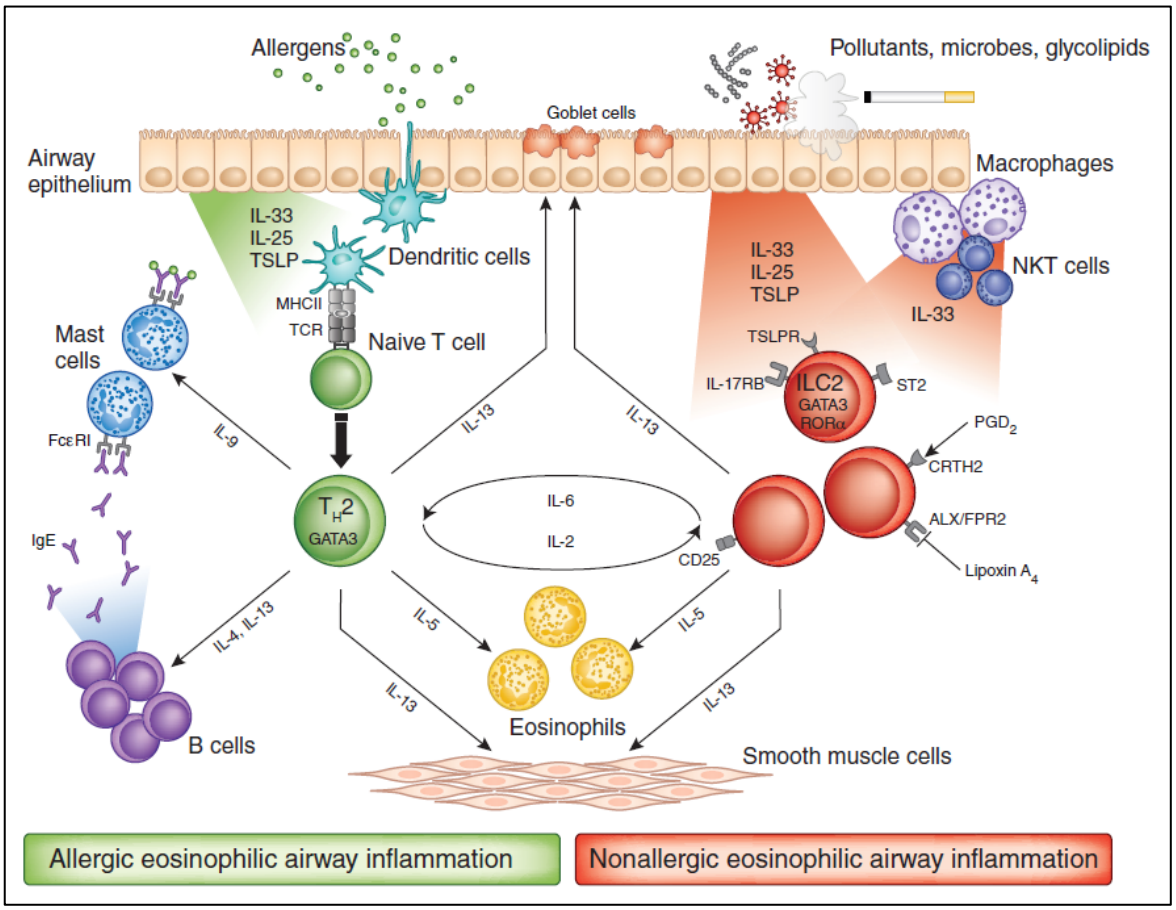

Figure 2: Pathways leading to eosinophilic and non-eosinophilic airway inflammation in asthma[15]
[Reprinted by permission from Springer Nature: Springer Nature; Nature Medicine: Eosinophils in the Spotlight: Eosinophilic airway inflammation in non-allergic asthma, Brusselle et al. © (2013)]

Over time, persisting Type 2 inflammation leads to remodelling of the airways. Airway walls thicken due to increase in airway smooth muscle, fibrosis of the airway wall, epithelial mucosa proliferation and mucosal inflammation and infiltration with inflammatory lymphocytes, eosinophils and mast cells. Figure 3 shows a cross section of a normal airway and an asthmatic airway[17]. Goblet cell proliferation and increase mucus productions leads to plugging of the small airways causing air trapping and hyperinflation[12,17]. In asthma, chronic inflammation, repeated epithelial injury and repair, and airway remodelling occur concurrently. However, superimposed on this process are episodes of acute worsening – asthma exacerbations.

During an exacerbation patients experience an acute worsening of airflow obstruction and asthma symptoms such as wheeze, breathlessness and chest tightness due to contraction of airway smooth muscle, airway wall oedema and mucus plugging[18]. While exacerbations lead to acute worsening in symptoms they are also associated with accelerated decline in lung function long term[19]. Type 2 airway inflammation predisposes to asthma exacerbations as the airways are hypersensitive to allergens or environmental stimuli and have an exaggerated response. Exacerbations lead to increased activation of the Type 2 inflammatory processes leading to further airway inflammation and remodelling[20]. There are multiple precipitants or triggers for asthma exacerbations such as allergens, pollution, exercise and drugs. However, the most common triggers for an exacerbation are respiratory viruses such as rhinoviruses, coronaviruses, influenza and respiratory syncytial virus[18].

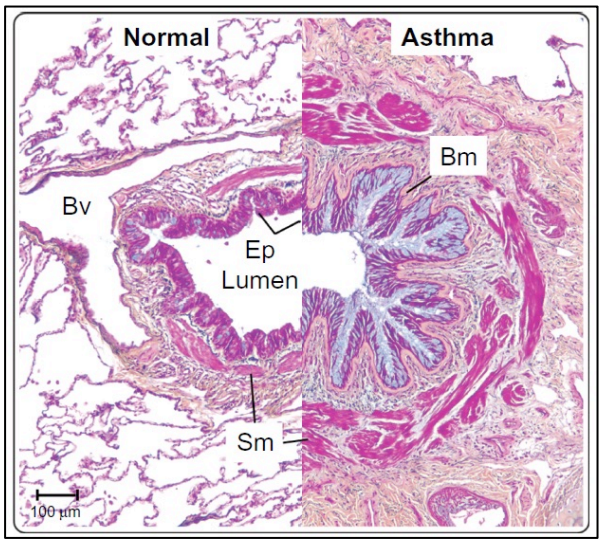

Figure 3: Structural remodelling of a medium sized airway in asthma[17]

Abbreviations: Bv blood vessel; Ep epithelium; Bm basement membrane; Sm smooth muscle.

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1.2. Pharmacological management of asthma

Management of asthma has evolved, today asthma treatment is directed by national and international guidelines which recommend a stepwise approach to asthma management[2,21].Understanding the pharmacological properties of corticosteroids and beta-agonists, asthma treatment regimens and guidelines is relevant to this thesis to appreciate how these drugs have their clinical effects, the role of long-acting $beta_2$-agonists (LABAs) and why symptom-driven budesonide-formoterol is a possible alternative management strategy in mild-moderate asthma.

1.2.1. History of asthma treatment

Whilst asthma was recognised by the ancient Greeks, it was Sir John Floyer who provided the earliest contemporary definition of asthma in his book *A Treatise of the Asthma* in 1698. As a physician and asthma sufferer, he proposed that bronchoconstriction contributed to asthma, he described asthma exacerbations and how his own symptoms were influenced by the seasons and the environment[22]. In 1860, Henry Hyde Salter published "On asthma, its pathology and treatment" which included a formal definition of asthma as well as vivid (and likely personal) descriptions of asthma exacerbations. Salter advocated hot strong coffee during asthma exacerbations[23], not an unreasonable suggestion given that a Cochrane review in 2010 concluded that caffeine was a modest bronchodilator[24]. In use by the late 1800s the first anticholinergic drugs to treat asthma came from belladonna alkaloids, often administered by smoking asthma cigarettes, but also as solutions or pastilles. They produced bronchodilation by inhibiting reflex bronchoconstriction via blockade of the acetylcholine receptors[25]. In 1910 Melland described effects of injecting adrenaline as "truly marvellous" for acute asthma[26] heralding the beginning of the era of beta-agonists to treat asthma symptoms. Inhalers containing adrenaline and isoproterenol (a relatively specific $beta_2$-agonist) were available from the 1950s. From the 1960s-1970s specific short-acting $beta_2$-agonists (SABAs) including salbutamol and terbutaline were developed and quickly became the primary treatment for asthma. LABAs were developed in the 1980s[25]. The first case series describing the use of

corticosteroids to manage asthma was in the 1950s. In the 1970s oral corticosteroids (OCS) were in common use for preventing and treating asthma exacerbations but were associated with significant side effects. The first large trial confirming the efficacy and equivalence of ICS compared with OCS in stable asthma was conducted by the British Thoracic Society (BTS) published in 1975[27] and signalled the start of the current paradigm in asthma management of ICS for prevention and SABA for relief. The Introduction of beta-agonists gave patients symptomatic relief, and the use of ICS allowed asthma to be controlled and exacerbations prevented.

1.2.2. Asthma guidelines and management

Increasing global prevalence of asthma combined with an epidemic of hospitalisations and deaths from asthma in the 1970s and 1980s led to the collaboration of healthcare professionals, governments and policymakers to produce guidelines on best practice for diagnosing and managing asthma. The first asthma guidelines were published in Australia and New Zealand in 1986. The BTS published theirs in 1990 and in 1993 GINA was formed[28]. The asthma guidelines current when the work of this thesis was commenced (including the 2016 New Zealand asthma guidelines and the GINA strategy for asthma management and prevention until 2019), advocated the following stepwise approach to asthma treatment[2,21]. Step 1 recommends SABA given as required in response to symptoms, next Step 2 recommends addition of regular low dose ICS in addition to SABA if the patient was experiencing asthma symptoms, required their SABA more than twice a week or had night waking due to asthma. If asthma symptoms were not controlled with regular low dose ICS or the patient had experienced an exacerbation then Step 3 recommends an increase in the dose of ICS or addition of other therapies such as LABAs, long-acting muscarinic antagonists or theophylline. The approach suggested by the 2018 GINA strategy is shown in Figure 4, and from the 2016 New Zealand asthma guidelines in Figure 5[2,21].

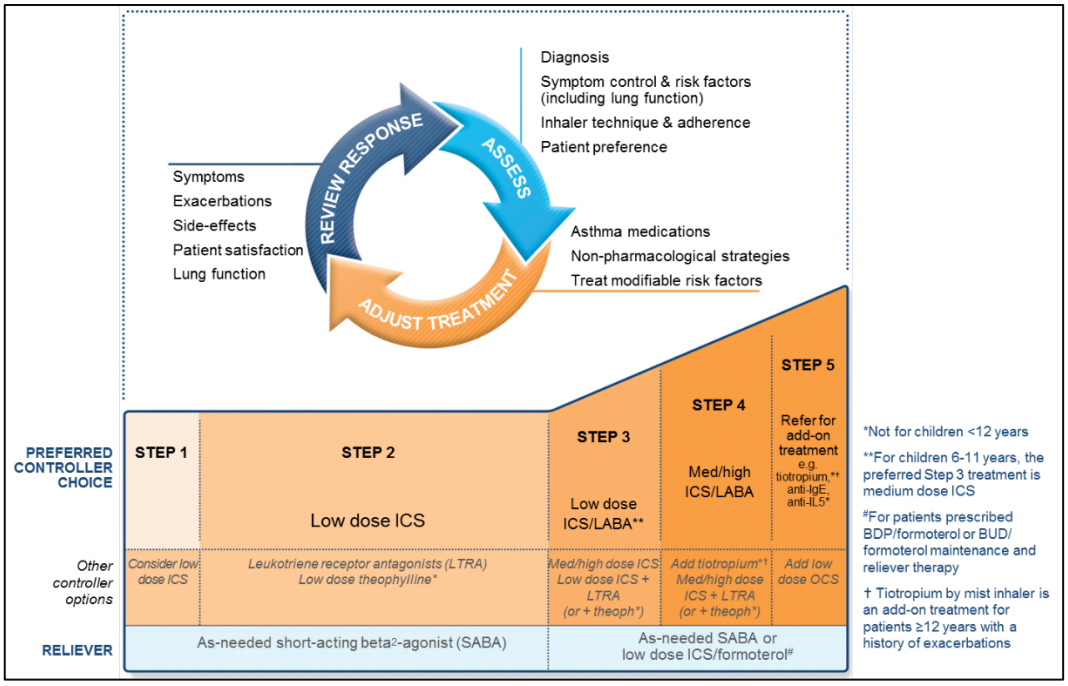

Figure 4: Global Initiative for Asthma 2018 stepwise approach to control asthma symptoms[2]

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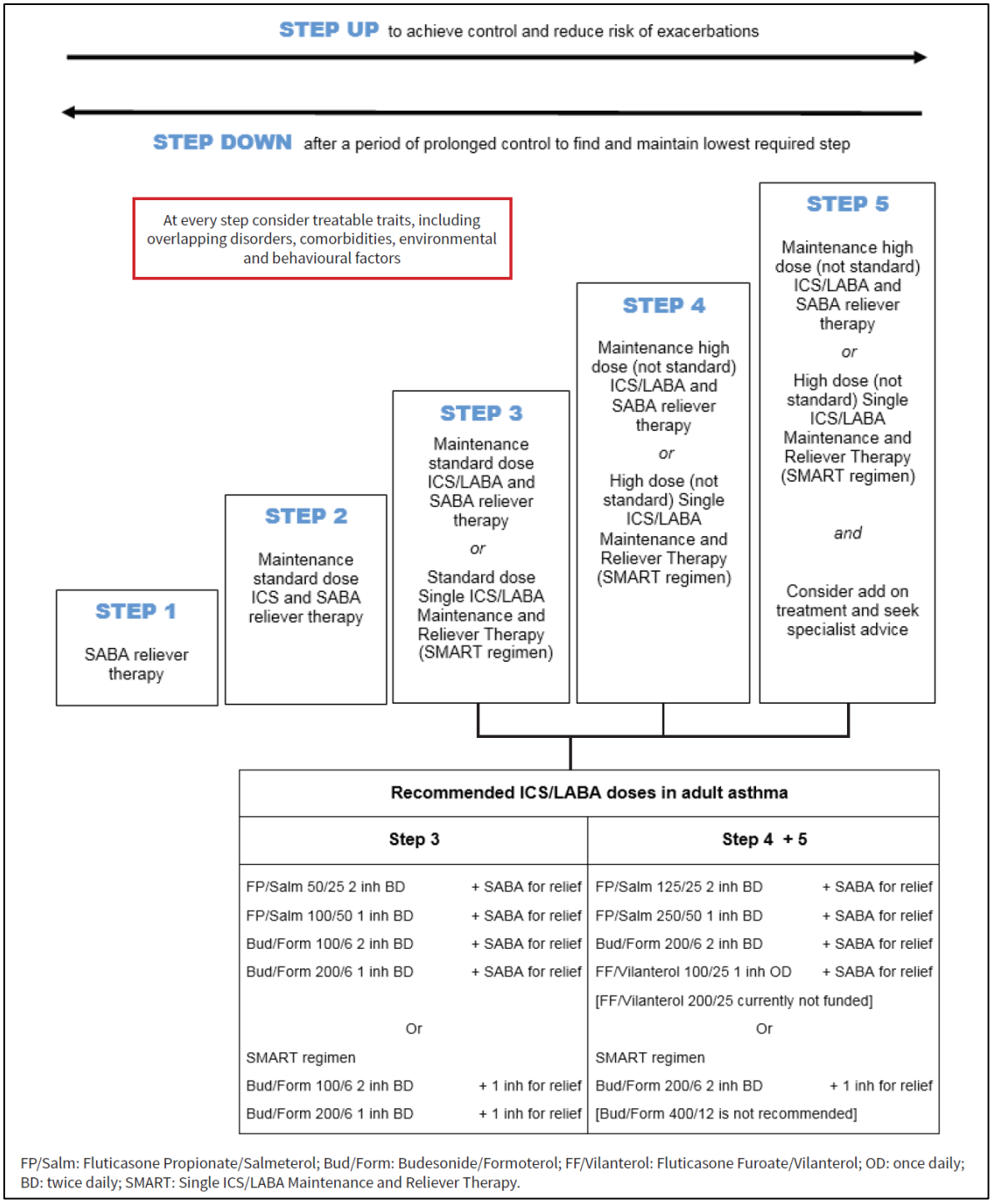

Figure 5: New Zealand adult asthma guidelines - stepwise approach to asthma management[21]

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1.2.3. Inhaled corticosteroids

1.2.3.1. Mechanism of action

Regular ICS are the cornerstone for most asthma treatment regimens. The clinical effects of ICS are exerted through their ability to reduce inflammation within the airways. ICS bind to glucocorticoid receptors (a nuclear receptor) which increases the transcription of anti-inflammatory cytokines and decreases the transcription of pro-inflammatory cytokines, chemokines and enzymes involved in the inflammatory response. In the airways this leads to a reduction in the recruitment and survival of inflammatory cells such as mast cells, eosinophils and lymphocytes[29]. ICS work topically, the target of ICS is the respiratory epithelium. Short term effects of ICS include reduction in eosinophils and airway hyper-responsiveness, which is detectable within six hours[30,31]. Medium term epithelial integrity is restored, however, reversal of airway remodelling and airway hyper-responsiveness may take several months[32].

1.2.3.2. Clinical effects and dosing

ICS have considerable clinical benefits in patients with asthma, particularly those with Type 2 inflammation[17]. Use of ICS reduces the frequency and severity of asthma symptoms, use of bronchodilators, airway hyper responsiveness, risk of asthma exacerbations and death from asthma. Patients on ICS have a higher peak expiratory flow rate (PEFR)[33–37]. Long term ICS has a protective role in slowing down decline in forced expiratory volume in 1 second (FEV_1) in patients with asthma[38,39].

There are several different types of ICS, however budesonide is the formulation used in the PRACTICAL study. Table 1 lists those that are available in New Zealand. Most ICS are prescribed twice daily, although fluticasone furoate is licenced to be taken once a day and clinicians may opt to prescribe other types of ICS once a day based on the characteristics and preferences of the patient in front of them. There are few studies comparing the efficacy of the different types of ICS[29], however they all exhibit a dose-response relationship[40]. Asthma guidelines recommend that ICS dose is increased until asthma is controlled and decreased following a prolonged period of good control[2,21].

However, if ICS is stopped completely symptoms often return and lung function declines[41]. In mild-moderate asthma much of the benefit from ICS is from low to moderate doses[40]. The top of the therapeutic efficacy dose-response curve for budesonide in mild asthma is around 400mcg per day where 80% of the benefit of inhaled budesonide is seen[42,43]. Higher doses of ICS do not provide any additional benefits in symptom control or improvements in lung function but are associated with an increased risk of side effects[40,42]. In patients with severe asthma, high doses of ICS may have a modest effect at reducing exposure to OCS, however, high doses do not have a significant effect on clinical outcomes[42]. This is relevant to this thesis as it suggests that high doses of budesonide are not required to control asthma. A patient with mild asthma using symptom driven budesonide-formoterol is unlikely to use ICS every day and doses lower than 400mcg per day of budesonide may be adequate to control mild-moderate asthma.

Table 1: List of the inhalers that contain ICS available in New Zealand

ICS formulation	Inhaler brand names
Fluticasone propionate	Flixotide, Floair, *Seretide & *RexAir
Budesonide	Pulmicort, *Symbicort & *Vannair
Beclomethasone dipropionate	Beclazone; Qvar
Fluticasone furoate	*Breo

*Also contains a LABA in the same inhaler. Constructed from information in Pharmac. Online Pharmaceutical Schedule - October 2019[44]

1.2.3.3. Side effects

Most side effects of ICS are from their local effects, however, some systemic absorption occurs through the lungs, oral mucosa and gastrointestinal tract[45]. Local side effects are usually mild but may still be troublesome and include hoarse voice, oral and pharyngeal candidiasis, pharyngeal inflammation and cough[46]. A meta-analysis of the systemic effects of ICS found all ICS have a dose-response relationship with systemic adverse effects, and fluticasone propionate has the greatest systemic bioavailability at higher doses[47]. ICS have the potential to cause adrenal suppression, and in rare instances the use of high dose ICS has precipitated an adrenal crisis when stopped suddenly[45]. They can lead to growth reduction in children, reduction in bone

mineral density, fractures, cataracts, glaucoma and skin bruising[45,48]. However, concerns over side effects need to be placed in clinical contexts and are almost always outweighed by the benefits of ICS in asthma.

1.2.4. Inhaled beta$_2$-agonists

1.2.4.1. Mechanism of action

Inhaled beta$_2$-agonists are used extensively for symptom relief in asthma. Their clinical effects come from their ability to reverse bronchoconstriction by inducing airway smooth muscle relaxation. In humans airway smooth muscle tone is primary mediated by acetylcholine release from parasympathetic neurones. There are no sympathetic neurones in the airways, so the sympathetic nervous system affects airway smooth muscle tone through the action of circulating catecholamines on the beta$_2$-adrenergic receptors on the surface of the smooth muscle cells and parasympathetic synapses[49]. Relaxation of airway smooth muscle is due to activation of beta$_2$-adrenergic receptors[50,51]. The beta$_2$-adrenergic receptor is a G protein coupled transmembrane receptor. Binding of a beta-agonists activates the associated G protein which in turn activates adenylyl cyclase which results in an increase in intracellular cyclic 3'5-adenosine monophosphate activating protein kinase A. Protein kinase A phosphorylates proteins such as myosin light chain kinase and reduces intracellular Ca^{2+} by promoting Ca^{2+}/Na^{+} exchange leading to smooth muscle relaxation[49].

Selective beta$_2$-agonists mimic the effect of adrenaline by binding to beta$_2$-adrenergic receptors on airway smooth muscles. Salbutamol and terbutaline are SABAs. They exert their effects within in 5 minutes and have a recovery time of 4-6 hours[51–53]. Therefore they are extensively used to relieve asthma symptoms. The most commonly used LABAs in clinical practice are formoterol and salmeterol. Both have a duration of action of at least 12 hours. Formoterol exerts its effects within 5 minutes and has an equivalent onset time to salbutamol, but salmeterol has an onset time of over 30 minutes[51,54]. This is relevant to this thesis because it means formoterol is suitable for symptom relief due to its fast onset of action, whereas salmeterol is not because the patient would not gain symptom relief for 30 minutes.

1.2.4.2. Clinical effects and dosing

SABAs are not considered to have anti-inflammatory properties, and are used to relieve symptoms caused by bronchoconstriction through relaxation of the smooth muscle surrounding the bronchi. Monotherapy with beta$_2$-agonists is only recommended for those with very mild asthma when SABAs are recommended for intermittent use for symptomatic relief[21]. SABAs are used as rescue therapy whereas LABAs are used in conjunction with ICS to reduce the burden of asthma symptoms without having to escalate doses of ICS[55,56]. The addition of a LABA to ICS improves lung function, symptom control and decreases rate of severe exacerbations compared to ICS monotherapy[57,58]. These effects only appear to be associated with LABAs, not SABAs[59]. The fast onset of action of formoterol has led to its use in combination with ICS in one inhaler as both maintenance and reliever therapy known as Single Maintenance And Reliever Therapy (SMART)[60–62]. ICS (budesonide) in combination with a fast-acting LABA (formoterol) in the Symbicort Turbuhaler, is already in use as reliever therapy as part of the SMART regimen. This meant budesonide-formoterol combination was a suitable choice to investigate the efficacy of a symptom-driven ICS-reliever regimen in mild-moderate asthma. Different asthma regimens will be discussed in more detail in section 1.3.

1.2.4.3. Side effects

Many of the side effects of beta$_2$-agonists are due to their actions on the beta-receptors expressed by other organs such as the heart, blood vessels and skeletal muscle. Action on the heart and blood vessels can lead to tachycardia, palpitations and vasodilation. Stimulation of the sodium/potassium ATPase pump coupled to beta-adrenoreceptors on skeletal muscle can lead to sequestration of potassium within muscle cells and hypokalaemia which, if severe enough can precipitate cardiac arrhythmias. Direct stimulation of the beta-adrenoreceptors in skeletal muscle can lead to tremor[61]. Side effects are related to dose, and so are most common when repeated doses of beta$_2$-agonists are taken during exacerbations of asthma[63].

1.2.4.4. Safety issues related to beta$_2$-agonists

The use of symptom-driven budesonide-formoterol in patients with mild-moderate asthma would lead to an increase in patients taking a LABA. Therefore, it is appropriate to acknowledge the safety concerns around the use of LABAs in asthma. The epidemics of death from asthma during the 1960s and 1970s in New Zealand, Australia, UK, USA, Germany and Canada suggested that the use of beta-agonists was associated with death from asthma[64,65]. The highly potent non selective beta-agonists isoprenaline and fenoterol were implicated[66,67]. The selective LABAs, formoterol and salmeterol were introduced in the 1990s. However, concerns were raised that use of formoterol or salmeterol without ICS increased the risk of severe exacerbations and masked airway inflammation[68], and unopposed use of salmeterol may be associated with an increase in mortality[69,70]. Despite several meta-analyses[71,72] a question still remained over the safety of LABAs in combination with ICS. In an attempt to put the issue to rest the Food and Drink Administration (FDA) in the USA mandated that the pharmaceutical industry conduct four large randomised controlled trials (RCTs) comparing the effect of ICS-LABA combination or ICS alone on major asthma related adverse events including hospitalisation, intubation and death[73]. While incidence of asthma related adverse events was not significantly different between the two groups, the question over increased mortality remained unanswered as there were only three asthma related intubations and two asthma related death across four trials of 36,010 participants – too small a number to be able to draw any conclusions[74]. For the purpose of this thesis this data is reassuring as it suggests that use of symptom-driven budesonide-formoterol is unlikely to be associated with an increase in major asthma related adverse events compared to maintenance budesonide plus terbutaline as needed.

1.2.4.5. Synergism between ICS and beta$_2$-agonists

Corticosteroids and beta$_2$-agonists have synergistic effect at a cellular level. Corticosteroids increase transcription of the beta$_2$-receptor genes[75] and enhance the activity of the beta$_2$-receptor by improving coupling of G proteins to the receptor[76]. In turn beta$_2$-agonists may improve the effect of corticosteroid by increasing

translocation of the glucocorticoid receptor from the nucleus to the cytoplasm[77]. Clinically ICS-LABA combination therapy reduces symptom burden and SABA use, reduces the requirement for higher doses of ICS, and reduces the risk of asthma exacerbations particularly in patients who are still symptomatic on high doses of ICS[78]. Therefore, the use of budesonide-formoterol in combination to manage mild-moderate asthma may provide additional benefits to using budesonide and terbutaline separately.

1.2.4.6. Therapeutic equivalence of formoterol and SABA

There is evidence that formoterol is a more potent bronchodilator than the SABAs. The relative therapeutic index between formoterol and terbutaline is one actuation of formoterol 6mcg/actuation is roughly equivalent to 2 actuations of terbutaline 250mcg/actuation[79–81]. When budesonide-formoterol is taken as reliever therapy only one actuation is recommended (for the 200/6mcg strength inhaler), whereas two actuations of a SABA such as terbutaline are usually recommended[21,82,83]. Clinical trials have shown that formoterol as reliever therapy reduces the time to first severe asthma exacerbation and improves FEV_1 compared to terbutaline taken as reliever therapy[80,84,85]. Providing further evidence that that formoterol has benefits over SABA beyond just longer duration of action.

In this section, I have summarised of the history of asthma management and explained how asthma management evolved, discussed the pharmacological properties of ICS and beta-agonists, and why ICS are used to prevent asthma symptoms and beta-agonists are used for symptom relief. Asthma guidelines current at the time of planning of this thesis focussed on use of daily ICS to prevent symptoms and exacerbations with $beta_2$-agonists taken as required for the relief of symptoms. This management strategy will be discussed further in the following section 1.3 along with evidence for symptom-driven budesonide-formoterol as a potential alternative in mild-moderate asthma. The pharmacological properties of budesonide and formoterol are supportive of symptom-driven budesonide-formoterol as a potential alternative regimen in mild-moderate asthma. This is because the majority of benefit from

budesonide is derived at lower doses, and formoterol is a more potent bronchodilator than terbutaline which also has beneficial effects on rate of asthma exacerbations.

1.3. Asthma treatment regimens

In this section I will explore why symptom-driven budesonide-formoterol is an alternative approach in mild-moderate asthma. I will do this through discussion of treatment regimens current at the time of planning of this thesis and how poor adherence to ICS limits the efficacy of these regimens which meant an alternative approach was needed. Finally, I will review the literature on the use of symptom-driven ICS-reliever therapy in asthma.

1.3.1. Guideline directed asthma treatment

Asthma management is guideline based, and recommends a stepwise approach to treatment (outlined in section 1.2.2, Figure 4 and Figure 5). At the time of planning this thesis, when a patient was first diagnosed with asthma, guidelines[2,21] recommended they were prescribed a SABA such as salbutamol or terbutaline taken in response to symptoms. Then twice daily low dose ICS was added in if the patient was experiencing symptoms or needing to use their SABA inhaler more than twice a week, followed by addition of ICS-LABA if asthma control was still inadequate.

The addition of a LABA to ICS has greater efficacy than increasing doses of ICS[55]. In the last five years a combination ICS-LABA inhaler containing fluticasone furoate and vilanterol has been licenced for use once a day use[86]. Combination ICS-fast acting LABA inhalers such as Symbicort which contains budesonide and formoterol can be used both as maintenance therapy to prevent symptoms and as reliever therapy in response to asthma symptoms (the SMART regimen)[87]. The same inhaler is taken daily and as-needed in response to asthma symptoms. The benefits of this approach will be discussed further in sections 1.3.2 and 1.3.3. However, the SMART regimen has been shown to reduce asthma exacerbations compared to ICS-LABA preventer therapy with SABA for symptom relief[88]. The fast onset of formoterol[60] allows budesonide-formoterol to be used as both a maintenance and reliever medication. In patients with moderate-severe asthma taking maintenance budesonide-formoterol, there is a reduction in exacerbations when budesonide-formoterol is used as reliever therapy

compared to when a SABA is used as reliever[87]. This supports the hypothesis that symptom-driven budesonide-formoterol may be an effective treatment regimen in mild-moderate asthma.

1.3.2. Adherence in asthma and the need for a new paradigm

Daily maintenance ICS is a highly effective treatment for asthma, but poor adherence to daily treatment is a key cause of adverse outcomes in asthma. Poor adherence to maintenance ICS is significantly associated with adverse outcomes in asthma including poor asthma control, a higher burden of asthma symptoms[89–94], a higher risk of severe asthma exacerbations[95,96], emergency department visits and hospitalisation due to asthma, OCS use[97], and death from asthma[8]. Symptom-driven budesonide-formoterol in mild-moderate asthma would circumvent the problem of poor adherence and underuse of ICS as the requirement for the patient to take an inhaler every day would be removed, but the patient would take ICS whenever they had asthma symptoms. The World Health Organisation (WHO) defines adherence as:

> *"The extent to which a person's behaviour – taking medication, corresponds with agreed recommendations from a health care provider."*[98]

With the implicit understanding that unlike "compliance", adherence requires the patient's agreement[99]. The WHO describes 3 patterns of non-adherence[98]:

i) Erratic non-adherence – the patient understands the importance of adherence and would like to take their medications as intended but factors such as forgetting, busy lives or not prioritising their asthma management prevent them from achieving this.

ii) Unwitting non-adherence – the patient has not understood, has misinterpreted, or has forgotten the instructions given to them.

iii) Intelligent non-adherence – the patient has deliberately decided to take their medications in a way other than directed. They may stop using them, reduce or increase the dosage but this reflects a reasoned choice[98].Patients

with asthma may choose to take their preventer inhalers only when they consider them necessary for example when they are experiencing a flare up in symptoms[100].

Poor adherence to medications is well recognised in many chronic diseases[98], however, adherence to asthma inhalers is lower than adherence to treatments for other chronic conditions such as diabetes, hypertension and breast cancer[101]. Asthma has some unique features that are not prevalent in other chronic diseases. A high proportion of patients with asthma are children, teenagers and young adults[102], so represent a different population to many with chronic disease. They have different patterns of medication use, adherence, and drivers of poor adherence[103,104]. Symptoms of asthma can come on quickly and patients strongly associate SABA use with quick relief[105]. Quick relief from symptoms is overwhelmingly what patients want from their inhalers, and perceptions of asthma control centres on management of asthma attacks, not on absence of day to day symptoms[106,107]. Patients are very familiar with titrating their use of SABA to their symptoms and often a SABA in the ubiquitous blue inhaler is the first treatment an asthmatic patient is given. Therefore, when they are prescribed ICS twice daily, it lacks the flexibility and control over the medication use that patients are familiar with[108].

SABAs do not address the underlying airways inflammation responsible for many of the patient's symptoms[109]. Overuse of SABA can lead to worsening of asthma and decreasing response to the drug[110,111]. Patients often recognise early warning signs that their asthma is worsening, but frequently the most common response to worsening symptoms is to increase use of SABAs particularly in the early stages. ICS use is increased to a lesser extent and often later[100,112]. ICS taken daily prevents asthma symptoms and exacerbations however as there is no immediate noticeable effect from taking ICS, so this is not the medication that patients perceive gives them the greatest benefit. It is not uncommon for patients to decrease their use of ICS or stop it entirely if they feel their asthma is under control[100]. Widespread lack of recognition of severity of asthma, along with the perception that asthma is not severe

enough to warrant twice daily medication and normalising of asthma symptoms by both patients and clinicians also contributes to poor adherence to ICS[100,106,107,113,114].

The clinician's view of well controlled asthma is the absence of asthma exacerbations, and minimal symptoms or reliever inhaler use [115]. This has been achieved in the setting of a clinical trial[116]. However, population based surveys of thousands of patients with asthma have shown that in the real world, level of asthma control falls short of these ideals as 45-51% of patients had uncontrolled asthma based upon reporting of asthma symptoms and 44-73% had experienced an exacerbation severe enough to warrant oral steroids in the preceding year[100,106,107,117]. Patients normalise their symptoms, overestimate their asthma control and underestimate the severity of their symptoms. Despite experiencing regular symptoms or having an exacerbation within the last year, many still consider their asthma to be well controlled[106,107,113]. Normalisation of asthma symptoms, under-recognition of their severity and the knowledge that SABA will provide a quick fix when needed impacts upon patients' perceptions of the necessity of their preventer inhalers[117]. Low perception of necessity and effectiveness of preventer inhalers, coupled with the inconvenience of taking them twice a day and the presence of an alternative in SABA used in response to symptoms means adherence to regular controller ICS is almost universally poor[118,119].

Methods for measuring use of and adherence to inhaled therapies will be discussed in section 1.4.1. Within the setting of a clinical trial, adherence to daily maintenance medication is variable and has been measured to be as low as 0% of prescribed doses in some participants[120] versus >80% of prescribed doses in others[121,122]. Poor adherence to ICS is common in clinical practice[123]. In population based surveys of medication use, patients report low levels of ICS use compared to SABA use. In one study, 23% of patients had used ICS in the preceding 4 weeks, but 63% had used a reliever inhaler[117], in another 14% reported taking their preventer inhalers every day and 62% reported using a reliever inhaler in the last week[106]. Dispensing data from pharmacies corroborates this narrative as more prescriptions for reliever inhalers are dispensed than preventer inhalers[124–129]. Poor adherence to preventer inhalers causes

an apparent increase in perceived asthma severity by both patients and clinicians which can lead to a patient's treatment being increased unnecessarily[130].

Epidemiological data on the benefits of regular ICS use and harms from overuse of SABA comes from the Canadian Saskatchewan database which followed 30,569 patients with asthma from 1975 to 1997. In this population, regular ICS reduced the risk of hospitalisation due to asthma[37], and death or near death from asthma[36,131]. Regular use of beta$_2$-agonists was associated with increased risk of death or near death from asthma[132], and patterns of increasing use of beta$_2$-agonists were predictive of a life threatening exacerbation of asthma[133]. This pattern was mirrored in the 2014 National Review of Asthma Deaths in the UK, "Why asthma still kills"[8]. This review found 86% of the patients who died had been prescribed ICS inhaler, but low repeat prescription dispensing rates indicated they were poorly adherent in the months preceding their deaths. However, patients had been dispensed a median of 10 SABA inhalers in the year prior to their death, highlighting the failure of the current treatment paradigm and lack of progress from the Saskatchewan database from the 1970s-1990s. Of note from the UK review of asthma deaths, 51% of those who died would have been classed as having mild or moderate asthma prior to their death, challenging the assumption that only those with the most severe disease die from asthma.

Understanding the reasons why a patient might be poorly adherent provides potential avenues to address poor adherence. There are multiple causes of poor adherence which may vary overtime and several causes may co-exist together. Discussed above, the WHO describes three patterns of non-adherence; erratic, unwitting and intelligent[98]. An alternative paradigm of non-adherence is to separate it into unintentional and intentional non-adherence[99]. Unintentional non-adherence incorporates the erratic and unwitting patterns described by the WHO. The patient intends to take their medication as prescribed but doesn't because of unintended factors such as forgetting, poor understanding or poor inhaler technique. Intentional non-adherence incorporates the WHO pattern of intelligent non-adherence, the patient has made an active decision not to take their medication as directed. The

distinction is helpful when considering factors that can be addressed to improve adherence. Causes of unintentional poor adherence can be addressed through education or reminders. However, to understand and address intentional poor adherence we need to explore patients' motivations and beliefs about their medications[99].

The necessities and concerns framework (Figure 6) is a model for understanding how adherence is influenced by the interplay between a patient's beliefs about the necessity of their medications versus their concerns over taking them[134,135]. For example poor adherence to ICS in some patients may be related to them holding low necessity beliefs about ICS as they do not provide immediately perceivable benefit, whereas SABA do provide immediate benefit, or patients may have both specific and general concerns about taking a medication that contains a steroid[136]. Necessities and concerns can be determined through the Beliefs about Medicines Questionnaire (BMQ)[134]. Significant correlations exist between adherence and beliefs about the necessity of medications, and concerns about medicines across several different chronic diseases[99]. High necessities scores correlate with higher adherence and higher concerns scores correlate with lower adherence. In asthma, necessities and concerns beliefs predict poor adherence more robustly than sociodemographic or clinical factors[118,135], and are correlated with adherence to ICS as assessed by patient self-reported, pharmacy dispensing data, and data from electronic inhaler monitors[137–142].

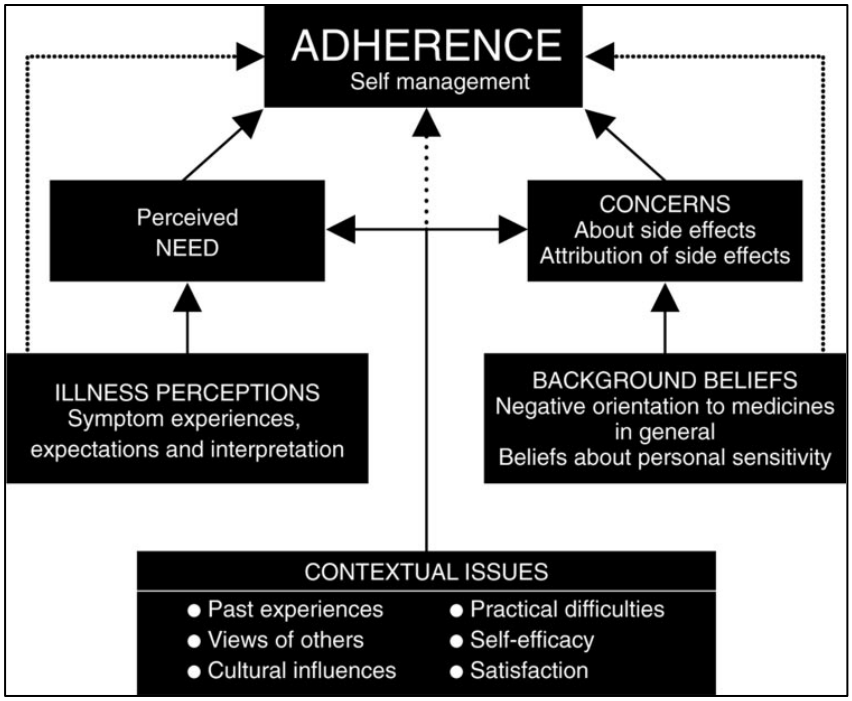

Figure 6: Necessities and concerns framework[99]

[Reprinted from Chest 130/1, Horne R, Compliance, Adherence and Concordance: Implications for Asthma Treatment page 71s, Copyright (2006), with permission from Elsevier.]

Any intervention to improve poor adherence would need to overcome the obstacles in a patient's life that contribute to unintentional non-adherences but also address their understanding of their medications, expectations and beliefs that underlie intentional non-adherence[115]. Providing generic information is unlikely to change someone's perceptions of their illness and their medication beliefs. Unless we can have an impact on patients' beliefs we are unlikely to change their behaviour[118]. RCTs of interventions to improve adherence to ICS in asthma have included psychological and education interventions; motivational interviewing; utilised electronic inhaler monitoring to track adherence, give reminders to take doses and provide feedback on usage; customised apps aimed to improve adherence; simplifying drug regimens; directly observed therapy and combinations of the above[143–147]. However, whether an intervention can change patients' behaviour and adherence to ICS particularly in the long term is uncertain. A Cochrane review on interventions to improve adherence to ICS in asthma concluded that while a variety of interventions can improve adherence they could not show that improved adherence affected clinical outcomes such as symptom burden or

exacerbation rate[143]. In addition, most studies on interventions to improve adherence to ICS ended after six months and it is unknown if the intervention had an effect beyond the study end. However, in one RCT investigating the use of reminders to improve adherence the participants had better adherence at 2 months than at 6 months[148], suggesting that initial improvements may not be maintained. A systematic review and meta-analysis of psychological interventions aimed at modifying health outcomes in asthma was unable to draw firm conclusions as to the benefit of psychological interventions in asthma[149]. A 2014 Cochrane review of effects of interventions to improve adherence in all chronic diseases concluded:

> *"Current methods of improving medication adherence for chronic health problems are mostly complex and not very effective"*[150]

The prevalence and subsequent burden of disease as a result of poor adherence to daily ICS in asthma, coupled with limited effectiveness of interventions to improve adherence means new approach is needed. In mild-moderate asthma the use of symptom-driven budesonide-formoterol is a possible alternative which would circumvent the problems of ICS underuse due to poor adherence. Patients would not be expected to take a medication every day, however, ICS would be taken when the patient was symptomatic as it is given in combination with their reliever. The evidence for symptom-driven ICS-reliever therapy in asthma will be reviewed next.

1.3.3. Evidence for symptom-driven ICS-reliever therapy in mild asthma

There is evidence from previous RCTs that symptom-driven ICS given either in combination with a $beta_2$-agonist or alone can be an effective strategy. This provides support for use of symptom-driven budesonide-formoterol in mild-moderate asthma. The combination of the two medications in one inhaler would avoid the problem of $beta_2$-agonists use and overused, unopposed by an ICS, particularly as patients preferentially use their reliever inhalers over their preventer inhalers during periods of stability but also in response to increasing symptoms and exacerbations[100]. The quick relief of symptoms provided by SABA is a strong motivational force that encourages

and reinforces their use. These factors contributed to interest in using a combination preventer and reliever inhaler to improve outcomes in asthma[13,151].

SABA use is correlated with asthma symptoms[152] and high SABA use is a strong predictor of risk of future adverse outcomes including severe exacerbations and poor asthma control[153]. When patients experience a worsening of their asthma symptoms they tend to self-medicate by overusing their reliever inhalers and may delay seeking medical review, irrespective of the frequency they are using their reliever inhalers[154]. There is evidence that prior to an asthma exacerbation, use of beta$_2$-agonists increases in parallel with asthma symptoms[155], this pattern of increasing beta$_2$-agonist use and delay in seeking medical review is repeated in patients prior to hospitalisation for asthma[112]. Patients who have had an asthma exacerbation are at increased risk of having another[156] however, following hospitalisation for an asthma exacerbation adherence to regular ICS in one population fell to 50% within seven days of discharge[157]. This highlights a window of opportunity to increase use of ICS particularly in response to worsening symptoms or exacerbations if it is given combination with beta$_2$-agonists, which use of symptom-driven budesonide-formoterol would address.

Due to peculiarities in drug licencing and pharmaceutical company practices, combination ICS-SABA inhalers are available in South America, but not in the rest of the world. Therefore, a combination ICS-SABA inhaler taken in response to symptoms was not a viable alternative strategy to the standard management of daily maintenance ICS plus a SABA as needed. Due to its fast onset time, formoterol provides rapid symptom relief and is an alternative to SABAs[51], because it is available in a combination inhaler with ICS (most commonly budesonide as Symbicort) budesonide-formoterol was the most appropriate drug combination to investigate a symptom-driven ICS-reliever regimen in mild-moderate asthma. In addition, the use of budesonide-formoterol as reliever therapy is already established in clinical practice as part of the SMART regimen for patients with moderate to severe asthma[21]. There is evidence that patients on the SMART regimen have a lower rate of asthma exacerbations, improved symptom control, improved lung function tests, better adherence to ICS and lower exposure to systemic corticosteroids compared to

patients taking regular ICS-LABA with SABA as reliever therapy [84,87,88,158–160]. This provides support for symptom-driven budesonide-formoterol as an appropriate alternative approach in mild-moderate asthma. Use of budesonide-formoterol reliever therapy in the SMART regimen allows flexible up-titration of ICS dose during periods of worsening asthma, which has the potential to lessen the severity or prevent exacerbations through early increases in ICS dose and reducing days of no ICS use.

Even patients with mild asthma have evidence of airway inflammation[161] and benefit from ICS[33,162], particularly if ICS are started soon after diagnosis[163]. In mild asthma, once daily low dose ICS reduces the risk of asthma exacerbations, lung function decline and improves symptom control, irrespective of frequency of asthma symptoms[164]. This suggests that all patients with mild asthma should receive low dose ICS. However, in mild asthma the intermittent nature of symptoms and under-recognition of their significance or severity means that commitment to a daily inhaler can be problematic[107,119,165]. Therefore, in patients with mild asthma, symptom-driven budesonide-formoterol without the expectation of daily use may be an attractive alternative. Population based surveys found that patients alter use of ICS in response to worsening symptoms[100], and an observational study of adherence to ICS in patients with mild-moderate asthma revealed three patterns of ICS use: regular; regular but at a lower than prescribed dose; and symptom-driven, with no significant difference in asthma outcomes in all three usage patterns[166]. However, this is not robust evidence that symptom-driven budesonide-formoterol is a safe and effective alternative to daily ICS with a SABA as required. The existing evidence from RCTs for symptom-driven ICS either in combination with a $beta_2$-agonist or alone in asthma will be reviewed next.

1.3.3.1. Systematic review of symptom-driven ICS in asthma

To identify RCTs that investigated symptom-driven ICS either in combination with a $beta_2$-agonist or alone Ovid was used to search Embase (1947-present) and Medline (1948-present) on 20th May 2019 using the following search strategy:

- 'Asthma' OR 'asthmatic' OR 'airways disease' (title-abstract-keyword)
- AND 'inhaled corticosteroid' OR 'ICS' (title-abstract-keyword)

- AND ‘as-needed’ OR ‘as-required’ OR ‘symptom-driven’

Results were limited to English language and RCTs. Titles and abstracts were screened and full texts of potentially relevant papers were obtained. RCTs which recruited children with wheezing illnesses, or participants with exercise induced bronchospasm but not a formal diagnosis of asthma were excluded.

The results of the search strategy are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram in Figure 7.

A summary of RCTs is provided in Table 2. A total of 12 relevant studies were identified of which three were concomitant to this thesis, but were published before this thesis was complete (these are the SYmbicort Given as Needed in Mild Asthma (SYGMA) 1 and 2 and Novel Symbicort Turbuhaler Asthma Reliever Therapy (START) studies).

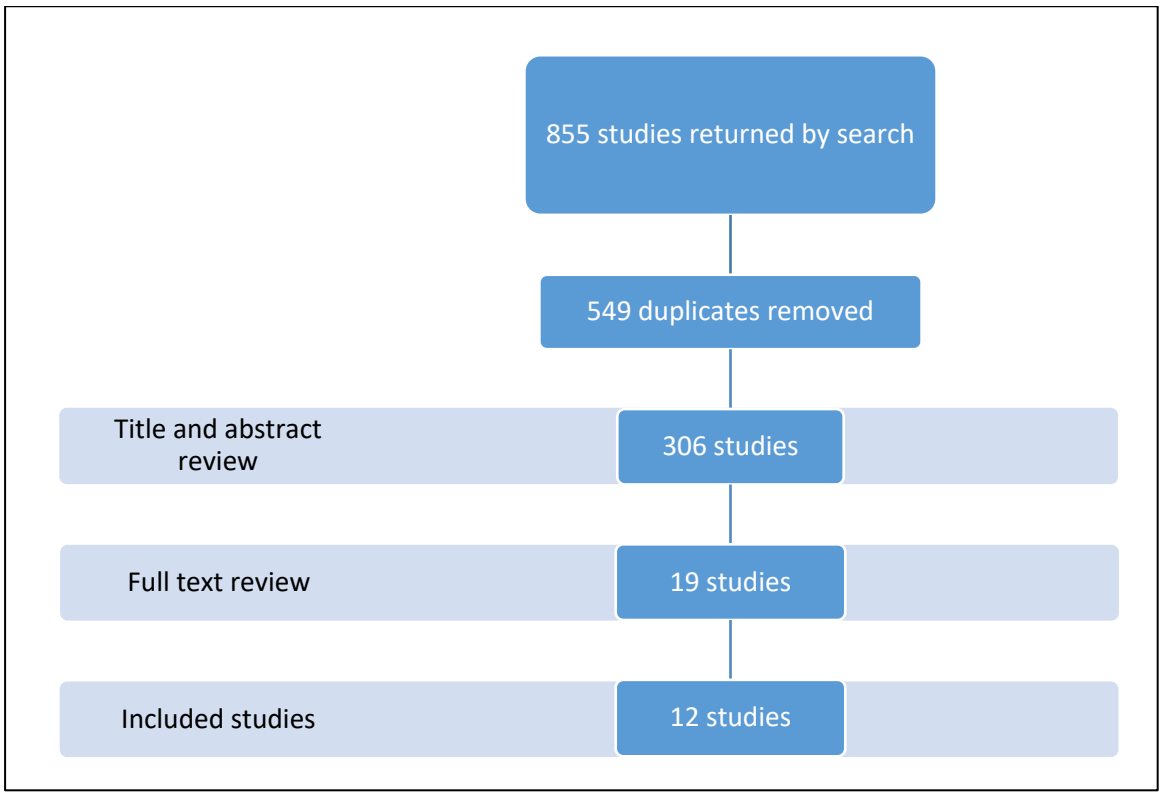

Figure 7: PRISMA diagram for systematic review of symptom-driven ICS in asthma

Table 2: Systematic review of symptom-driven ICS in asthma

Paper	Randomised treatments	Study overview	Outcomes
Boushey 2005 (IMPACT study)[167]	- Twice daily placebo (symptom-driven ICS arm) - Twice daily budesonide - Twice daily zafirlukast All participants received an additional course of budesonide or OCS for worsening symptoms	1 year, 255 adults with mild asthma	Similar PEFR and rates of asthma exacerbations in all 3 arms. The symptom-driven treatment arm took significantly less medication. Concluded it may be possible to treat mild asthma with short intermittent courses of inhaled or oral steroids.
Haahtela 2006 (SOMA study)[168]	- As-needed budesonide-formoterol - Formoterol as needed	24 weeks, 92 adults with mild asthma using SABA only	The as-needed budesonide-formoterol arm had a reduction in FeNO, higher FEV_1 and less frequent use of medication. Concluded that as-needed ICS-$beta_2$-agonist was more effective than $beta_2$-agonist alone.
Papi 2007 (BEST study)[169]	- As-needed beclomethasone-salbutamol - As-needed salbutamol - Twice daily beclomethasone + salbutamol as needed - Twice daily beclomethasone-salbutamol + salbutamol as needed	6 months, 455 adults with mild asthma	Similar rates of exacerbations and PEFR between as-needed beclomethasone-salbutamol arm and the two maintenance beclomethasone arms. Cumulative dose of beclomethasone lower in the as needed group. All outcomes were better with the beclomethasone arms than the salbutamol only arm. Concluded that symptom-driven beclomethasone-salbutamol was effective at a lower cumulative ICS dose.
Turpeinen 2008[170]	- Initially daily budesonide then as needed for exacerbations - Daily budesonide - Daily sodium cromoglycate	18 months, 176 children, newly diagnosed asthma	Daily budesonide resulted in significantly fewer exacerbations. Number of symptom free days was similar between both daily and as-needed budesonide. More side effects with daily budesonide. Concluded that regular budesonide lead to better control but with higher side effects and some children do not require continuous daily budesonide.

Paper	Randomised treatments	Study overview	Outcomes
Sposato 2010[171]	- Intermittent ICS+LABA - Regular ICS+LABA	4 years, 156 adults with persistent asthma taking ICS +/- LABA attending a respiratory outpatient clinic	Fewer exacerbations, asthma symptoms and less SABA use in the regular group. Concluded that regular use of ICS+LABA was superior to intermittent ICS+LABA.
Martinez 2011 (TREXA study)[172]	- Beclomethasone-salbutamol as needed - Beclomethasone twice daily + beclomethasone-salbutamol as needed - Beclomethasone twice daily plus salbutamol as needed - Salbutamol as needed	44 weeks, 843 children and adolescents, were allowed to be using low dose ICS on entry	Frequency of exacerbations was lower in groups taking daily beclomethasone. The as needed salbutamol group had the highest rate of exacerbations and treatment failure. Concluded that daily ICS was the most effective regimen to prevent exacerbations but use of as-needed ICS may be an appropriate step down regimen which may avoid side effects such as growth impairment.
Calhoun 2012 (BASALT study)[173]	- ICS taken whenever salbutamol was taken (as needed group) - Regular ICS, dose adjusted by physician every 6 weeks - Regular ICS, dose adjustments based on FeNO every 6 weeks	9 months, 342 adults with mild or moderate asthma well controlled on low dose ICS	No significant difference in time to treatment failure in all 3 groups. Treatment failure rates were equivalent in all three groups. Cumulative dose of ICS was significantly lower in the as needed group. Concluded that no regimen was superior.
Papi 2015 (AIFASMA study)[174]	- As-needed budesonide-formoterol - Twice daily budesonide-formoterol + terbutaline as needed.	1 year, recruited 866 adults with moderate asthma, uncontrolled with low dose ICS	Similar low incidence of severe exacerbations in both arms. Higher probability of and shorter time to treatment failure in as-needed arm. Concluded that as needed therapy was less effective than twice daily therapy in patients with moderate asthma uncontrolled on low dose ICS.

Paper	Randomised treatments	Study overview	Outcomes
Fitzpatrick 2016[175]	- As-needed ICS + salbutamol - Daily ICS	48 weeks, 300 toddlers taking ICS. Cross over trial	Daily ICS was associated with fewer asthma exacerbations and more days of asthma control. Response was predicted by allergen sensitization and blood eosinophils. Concluded that phenotyping for evidence of Type 2 inflammation was useful for guiding treatment and selecting those who will benefit most from daily ICS.
O'Byrne 2018 (SYGMA 1)[176]	- As-needed budesonide-formoterol - Budesonide twice a day plus as-needed terbutaline - As-needed terbutaline	1 year, 3836 adults and adolescents with mild asthma	As-needed budesonide-formoterol led to more weeks of well controlled asthma than as-needed terbutaline, but fewer than maintenance budesonide. The rate of severe exacerbations was similar for as-needed budesonide-formoterol and maintenance budesonide and lower than for as-needed terbutaline. Dose of ICS was significantly lower in the as-needed budesonide-formoterol arm. Concluded that as-needed budesonide-formoterol was superior to as needed terbutaline but inferior to maintenance budesonide.
Bateman 2018 (SYGMA 2)[177]	- As-needed budesonide-formoterol - Budesonide twice a day plus as-needed terbutaline	1 year, 4176 adults and adolescents with mild asthma	Equivalent rate of severe exacerbations in both treatment arms. Dose of ICS was significantly lower in the as-needed budesonide-formoterol arm. Control of asthma symptoms (measured by ACQ-5) favoured maintenance budesonide but this was below the minimally clinically important difference. Concluded that as-needed budesonide-formoterol was non-inferior to maintenance budesonide.

Paper	Randomised treatments	Study overview	Outcomes
Beasley 2019 (Novel START)[178]	- As-needed budesonide-formoterol - Budesonide twice a day plus as-needed salbutamol - As-needed salbutamol	1 year, 675 adults with mild asthma taking SABA only at randomisation	Exacerbation rate was lower in the as-needed budesonide-formoterol group than the salbutamol group and equivalent to the maintenance budesonide group. Severe exacerbation rate was lower in the as-needed budesonide-formoterol group than the other two groups. Dose of ICS was 50% lower in the budesonide-formoterol group than the maintenance budesonide group. Data suggested that as-needed budesonide-formoterol may be superior to maintenance budesonide. Concluded that as-needed budesonide-formoterol was superior to as-needed salbutamol.

Twelve RCTs were identified which randomised patients to either intermittent ICS use or regular maintenance ICS use. Three studies exclusively recruited children[170,172,175]. Nine studies were conducted in adults of which three were concomitant to this thesis[176–178].

In children[170,172,175] daily maintenance ICS was associated with better outcomes than symptom-driven ICS but this came with a higher risk of side effects such as growth retardation. As-needed ICS was considered to be appropriate in selected children or as step down treatment. SABA only regimens were inferior to regimens that used ICS either intermittently or regularly.

Of the six studies in adults published before the work of this thesis commenced, four recruited patients with mild-moderate asthma; the IMPACT, SOMA, BEST and BASALT studies[167–169,173]. Participants in these studies were randomised to symptom-driven ICS (either alone or in combination with reliever therapy) or to daily maintenance ICS or as-needed beta$_2$-agonist alone for symptom relief. In these studies, as-needed ICS-reliever therapy was superior to beta$_2$-agonist reliever therapy alone with respect to FeNO, FEV_1, PEFR, and exacerbation rate. Cumulative dosing of ICS was significantly lower in as-needed ICS groups compared to maintenance ICS groups. PEFR, exacerbation rate, and treatment failure was similar between as-needed ICS groups and maintenance ICS groups leading the study authors to conclude that symptom-driven ICS was effective in mild asthma at lower cumulative doses of ICS than maintenance ICS regimens.

Two of the studies recruited patients with moderate asthma. Sposato et al.[171] recruited patients from an outpatient respiratory clinic and included participants who were taking LABA at randomisation. Indicating this patient population had more severe asthma than participants in the other studies. Patients were randomised to intermittent ICS-LABA or regular ICS-LABA and followed for up to four years. The investigators found the regular group had fewer exacerbations and asthma symptoms than the intermittent group. The AIFASMA study[174] recruited patients with moderate asthma uncontrolled on low dose ICS and randomised them to either as-needed

budesonide-formoterol or twice daily budesonide-formoterol plus as-needed terbutaline. Both groups had a similar low rate of severe exacerbations however, there was a higher rate of treatment failure in the as-needed group leading the authors to conclude that in moderate asthma twice daily budesonide-formoterol was more effective than as-needed budesonide formoterol.

The SYGMA 1 and 2 studies[176,177] and the Novel START (Symbicort Turbuhaler Asthma Reliever Therapy) study[178] investigated as-needed budesonide-formoterol in mild asthma compared to daily maintenance budesonide with as-needed SABA. SYGMA 1 and Novel START also included an as-needed SABA only group. These three studies were running concurrently to the RCT in this thesis (the PRACTICAL study). Together, these four studies were designed to complement each other[151]. Evidence from the IMPACT, SOMA, BEST and BASALT studies suggested symptom-driven ICS-reliever therapy may be an alternative to twice daily ICS with SABA reliever therapy recommended by guidelines for mild asthma[2,21]. Therefore, the use of as-needed ICS-reliever in mild asthma was identified as a research priority in the hope in that mild asthma it may avoid adverse outcomes due to inappropriate ICS underuse and SABA overuse[13,108]. The SYGMA studies were tightly controlled double-blind regulatory studies whereas the Novel START and PRACTICAL studies were “real world” studies designed to be generalisable to more patients with mild asthma in clinical practice[179].

The SGYMA 1 and 2 studies[176,177] were published in 2018. They recruited patients aged 12 and older with mild asthma taking SABA for relief of symptoms with or without maintenance low dose ICS. Between the two studies 8,012 participants were included in the final data set. Participants were randomised to either as-needed budesonide-formoterol; or twice daily budesonide plus as-needed terbutaline. In SYGMA 1 there was a third arm of as-needed terbutaline alone. SYGMA 1 reported that as-needed budesonide-formoterol was superior to as-needed terbutaline with respect to control of asthma symptoms and rate of severe exacerbations. In the SYGMA 1 study as-needed budesonide-formoterol was inferior to maintenance budesonide with respect to asthma control, as patients taking as-needed therapy had 10% fewer well controlled asthma weeks. However, rate of severe asthma exacerbations was similar

between the as-needed and maintenance budesonide arms. Those taking as-needed budesonide-formoterol used 83% less ICS than those taking maintenance therapy. SGYMA 2 reported as-needed budesonide-formoterol was non-inferior to maintenance budesonide with respect to severe asthma exacerbations. However, asthma symptoms as measured by the Asthma Control Questionnaire-5 (ACQ-5)[180] was 0.11 units lower in the maintenance budesonide arm indicating asthma symptom were better controlled with maintenance budesonide, but the difference was less than the minimal clinically important difference of 0.5. The as-needed budesonide-formoterol group used 75% less ICS than the maintenance budesonide group.

The Novel START study[178] reported in 2019, was the first of the open label "real world" studies, the PRACTICAL study (the RCT in this thesis) is the second. 675 participants were randomised to as-needed budesonide-formoterol, or twice daily budesonide plus as-needed salbutamol or as-needed salbutamol alone. The Novel START study found as-needed budesonide-formoterol was equivalent to maintenance budesonide with respect to exacerbation rate however, it was superior to maintenance budesonide with respect to severe exacerbation rate. Mirroring the findings of SYGMA 2, ACQ-5 was lower in the maintenance budesonide arm, again this was below the minimal clinically important difference and the as-needed budesonide-formoterol group used 50% less ICS than the maintenance budesonide group. As-needed salbutamol was inferior to both budesonide containing regimens for all outcomes.

Discussed in this section, evidence from the SMART studies showed budesonide-formoterol reliever therapy leads to fewer exacerbations and better asthma control than SABA reliever therapy in patients with moderate to severe asthma taking maintenance budesonide-formoterol[181]. Therefore, it would seem logical that symptom-driven budesonide-formoterol would be a superior to SABA monotherapy in patients with mild asthma as was shown by the SYGMA 1 and Novel START studies. Evidence from the SOMA study[168], post-hoc analysis of the START study[164], SYGMA 1[176] and Novel START[178] along with epidemiological data on SABA[132] use reveal that SABA only regimens are associated with worse asthma outcomes than regimens that use ICS, even in patients with very mild intermittent asthma. Therefore, managing asthma

just with SABA monotherapy should be discouraged. Moving from daily maintenance ICS to symptoms driven budesonide-formoterol represents a paradigm shift in the treatment of mild-moderate asthma. The present evidence from two RCTs[171,174] suggests that in moderate to severe asthma, symptom-driven budesonide-formoterol may not be an appropriate regimen and daily maintenance treatment is required. However, in mild asthma the IMPACT[167], SOMA[168], BEST[169], BASALT[173], SYGMA 1 and 2 studies[176,177] suggest that symptom-driven ICS may be non-inferior to maintenance ICS, whilst the Novel START study[178] suggests that it may be superior.

The PRACTICAL study (chapter 2) aims to extend the findings of The SYGMA 1 and 2 and Novel START studies to patients with mild-moderate asthma. In addition the use of a real world open label study design will address issues of generalisability in the SYGMA studies due to their highly controlled regulatory nature.

1.4. Use of inhalers in asthma and electronic inhaler monitoring.

Evidence from the SYGMA 1 and 2 and Novel START studies showed symptom-driven budesonide-formoterol was effective at lower exposure to ICS than maintenance budesonide plus as-needed SABA. However, the mechanism of how this effect is achieved is unclear. It has been suggested that timing of ICS dosing may be more important in averting asthma exacerbations than total exposure[177,178]. If a patient is taking ICS in response to symptoms they will naturally up-titrate their dose at times of asthma worsening and then down titrate it when their asthma is stable. In addition, use of formoterol as bronchodilator rather than a SABA may be providing further benefits. This section will explore how inhaler use can be quantified and the literature on patterns of inhaler use.

1.4.1. Methods of measuring use of inhalers in asthma and electronic inhaler monitoring.

In many RCTs, adherence to and patterns of use of study medications are not quantified so time and dose dependent actions are not known[182]. The PRACTICAL study was designed to mimic the real world where adherence to maintenance medication is poor. Information on dosage and timing of inhaler use is important as it would provide data on differences in usage between symptom-driven budesonide-formoterol and maintenance budesonide plus as-needed terbutaline. This may provide an explanation why significantly lower exposure to ICS in the as-needed budesonide-formoterol groups in the SYGMA 1 and 2 and Novel START studies was associated with a similar or lower rate of severe exacerbations to maintenance budesonide plus as-needed SABA.

Several different methods have been used to quantify use of inhalers in asthma. Methods to measure use and adherence to asthma inhalers can be broadly divided into subjective and objective measures. Knowledge of the strengths and weaknesses of the different methods to quantify inhaler use is required to select the most

appropriate method to quantify inhaler use and determine patterns of use. Table 3 summarises the different methods used in the literature to quantify inhaler use, references studies that have used these methods and outlines the strengths and weaknesses of each method.

Table 3: Methods of measuring inhaler use

Method	Examples of use	Strengths	Weaknesses
Subjective methods			
Recall/patient interview	[157,183–188]	Simple and low cost to administer Can provide information on reasons for use and poor adherence	Inaccurate Strongly affected by recall and desirability bias Does not give reliable information on patterns of use Correlates poorly with inhaler use measured by electronic inhaler monitors Patients tend to overestimate use of preventer medications and underestimate use of reliever medications
Patient Diaries	[189–195]	Less affected by recall bias if completed in a timely fashion	Inaccurate Affected by desirability bias Variable correlation with inhaler use measured by electronic inhaler monitors Tendency to over report use of preventer medications, examples of both under and over reporting of reliever medication use
Validated questionnaires	[118,130,196–198]	May address barriers to adherence as well as actual adherence behaviour	Unable to accurately determine adherence Cannot quantify patterns of inhaler use
Clinician assessment	[130,188,199]	Easy to incorporate into clinical assessment Can explore reasons for use, poor adherence and patterns of use	Very poor at estimating adherence Cannot quantify patterns of inhaler use

Method	Examples of use	Strengths	Weaknesses
Objective methods			
Canister weight	[122,157,183–185,200–202]	Simple in theory Objective More accurate than subjective measures	Requires highly accurate scales and adjustment for different medications Unable to detect patterns of use Subjective to dose dumping Overestimates adherence to preventer medication when compared to data from electronic inhaler monitors
Dose counter	[193,198,203–206]	Simple to conduct Objective	Only possible for inhaler devices that incorporate an accurate dose counter Less technical than using canister weights Unable to detect patters of use Subjective to dose dumping Overestimates adherence to preventer medication when compared to data from electronic inhaler monitors
Prescription dispensing	[125,198,199,202,207–209]	Objective Can provide population based and long term data so useful for epidemiological studies Relatively simple and low cost Can provide information on ICS and beta$_2$-agonist use	Does not necessarily correlate with number of doses taken, may be affected if patients use multiple pharmacies or stockpile medications Tendency to overestimate adherence to preventer medication when compared to data from electronic inhaler monitors
Electronic monitoring	[173,176,177,185,210,211]	Gold standard for quantifying adherence Provides information on time and date of use and therefore patterns of use Detects dose dumping Allows adherence to be corrected for the right dose being taken at the right time Some devices can provide information on inhaler technique	High cost and may require additional infrastructure, requires patient and staff training If patients are aware they are being monitored it may affect their behaviour Makes inhalers more bulky Potential for damage or device malfunction leading to data loss Potential privacy issues if health related data is uploaded to a third party

1.4.1.1. Use of electronic inhaler monitors in clinical trials

Table 3 demonstrates that electronic inhaler monitors are the best method to objectively determine detailed and accurate information on adherence and patterns of inhaler use. Therefore, they are the most suitable method for determining patterns of inhaler use and exposure to ICS and beta$_2$-agonists in patients using symptom-driven budesonide-formoterol or maintenance budesonide plus terbutaline as needed.

Measurement of adherence or use of a medication is important because unknown poor adherence in clinical drug trials creates data that is misleading and affects subsequent hypothesis testing and effect sizes. The International Society for CNS Clinical Trial Methodology Working Group on Nonadherence in Clinical Trials calculated that if 20% of participants are poorly adherent and contribute non-informative data then trial sample size would need to be increased by 60%[182]. Electronic inhaler monitors time and date stamp every actuation so intentional deception such as dose dumping, where the participant actuates the inhaler multiple times in quick succession can be detected[201]. Differences between treatment arms in a RCT can be examined to look for variation in usage and dose taken. The use of electronic inhaler monitors within a clinical trial adds strength and validity to the study conclusions on the effect of a particular treatment. They provide a wealth of additional information on patterns inhaler use in different scenarios[153] and characterise inhaler use during asthma exacerbations and quantify reliever inhaler overuse[112,152] which allows different predictors of future risk to be highlighted[212].

There are several different types of electronic inhaler monitors currently available, the properties of which are summarised in Table 4. Electronic inhaler monitors work by externally attaching to the inhaler. Most detect pressure or movement as the inhaler is used, however one device (the INCA device) uses audio to detect inhaler use[213]. The Doser, INCA, SmartTouch and SmartTurbo have all been validated during bench testing

to confirm their accuracy at recording inhaler use. The choice of electronic inhaler monitor is dictated by local availability and if the electronic inhaler monitor is compatible with the inhaler device used. For the work of this thesis the SmartTurbo electronic inhaler monitor manufactured by Adherium was used because they have previously been validated to have 99.9% accuracy[214,215], and are compatible with the Turbuhaler inhaler device which the medications used in this thesis come in (Symbicort Turbuhaler, Pulmicort Turbuhaler and Bricanyl Turbuhaler).

Table 4: Available electronic monitoring devices

Electronic monitor	Company	Description	Compatible inhaler devices	Accuracy
Doser	Meditrack Products, Easton, MA	Easily attaches to the top of metered dose inhalers Records the number of inhalations in a 24 hour time period but actuations are not time stamped Stores 30 days' worth of data	Metered dose inhaler	94.3-100% [216–218]
INCA	Trinity Centre for Bioengineering, Trinity College Dublin.	Externally attaches to inhaler Uses a microphone to detect inhaler use, actuations are time and date stamped Can use the audio files to assess inhaler technique as well as adherence	Accuhaler	89%[213]
Propeller	Propeller Health, Madison, Wisconsin	Stores up to 3,900 actuations and transmits the data via Bluetooth Records geographic location of use, as well as time and date[219]	Metered dose inhaler, Accuhaler, Elipta, Respimat	Unpublished bench testing data [220,221]
SmartTouch SmartTurbo	Adherium, Auckland NZ	Externally attaches to inhaler Records time and date of every actuation	Metered dose inhaler, Turbuhaler	99.9% [214,215]

1.4.2. Patterns of inhaler use

1.4.2.1. Cumulative inhaler use and use during periods of stability

The SYGMA 1 and 2 and Novel START studies[176–178] utilised electronic inhaler monitors to quantify use of ICS and beta$_2$-agonists in all treatment arms. Data from these studies on cumulative usage of budesonide is relevant to this thesis as it demonstrated that daily ICS dose was lower in the as-needed budesonide-formoterol group compared to the maintenance budesonide group ranging from 30% to 48% of the dose taken by the maintenance budesonide group. Table 5 presents the mean and median daily ICS dose in all three studies. In these three studies, lower usage of ICS in the as-needed budesonide-formoterol groups did not lead to an increase in asthma exacerbations. In the SYGMA 1 and 2 studies as-needed budesonide-formoterol was non-inferior to maintenance budesonide plus SABA as needed with respect to rate of severe exacerbations, but superior in the Novel START study. This suggests in patients with mild asthma, total dose of ICS is not the most important determinant of risk of exacerbations and other factors such as patterns of use or timing of use may be important.

Table 5: Daily ICS exposure during the SYGMA 1 and 2, and Novel START studies

Study & Randomised treatment	Mean (SD) daily ICS dose mcg	Median (IQR) daily ICS dose mcg
SYGMA 1		
As-needed budesonide-formoterol 200/6mcg	93 (102)	57 (50 to 65)
Twice daily maintenance budesonide 200mcg	315 (89)	340 (332 to 347)
SYGMA 2		
As-needed budesonide-formoterol 200/6mcg	104 (109)	66 (61 to 71)
Twice daily maintenance budesonide 200mcg	251 (118)	267 (257 to 272)
Novel START		
As-needed budesonide-formoterol 200/6mcg	107 (109)	73 (31 to 146)
Twice daily maintenance budesonide 200mcg	222 (113)	247 (132 to 314)

Table constructed from data in the primary manuscripts and supplementary appendices for the SYGMA 1[176], SYGMA 2[177] and Novel START studies[178]

The Novel START study was the only study to provide information on beta$_2$-agonist use (Table 6). Participants were directed to take two actuations of salbutamol for relief but only one of budesonide-formoterol. Daily actuations of beta$_2$-agonist were slightly higher in the as-needed budesonide formoterol group than the maintenance budesonide group. However, when the therapeutic ratio of formoterol to salbutamol[222] and the directions to participants to take one actuation of budesonide-formoterol for relief but two actuations of salbutamol is considered, use of beta$_2$-agonist was double in the budesonide-formoterol group compared to the budesonide maintenance group and roughly equivalent to use in the salbutamol group.

Table 6: Beta$_2$-agonist use in the Novel START study

Randomised treatment	Mean daily beta$_2$-agonist actuations	Median daily beta$_2$-agonist actuations
As-needed budesonide-formoterol 200/6mcg	0.53 (0.54)	0.37 (0.15 to 0.73)
Twice daily maintenance budesonide 200mcg with salbutamol as needed 100mcg	0.52 (1.03)	0.18 (0.06 to 0.46)
As-needed salbutamol 100mcg	1.01 (1.60)	0.50 (0.18 to 1.18)

Table constructed from data in the primary manuscript of the Novel START study[178]

While the SYGMA and Novel START studies provided cumulative information on ICS use and the Novel START study provided data on beta$_2$-agonist use, they have not provided data on patterns of use or inhaler use around asthma exacerbations. This is an important gap in the literature as this data may explain how a symptom-driven ICS-reliever regimen has its clinical effects.

Electronic inhaler monitors have been used in many different contexts however, data from the wider literature only provides limited information on patterns of inhaler use in asthma. Some studies report exposure to ICS[160], others just report adherence to ICS[223], and definitions or calculations of adherence differ between studies[223,224]. From study to study reported adherence to maintenance medications varies. The relevance and interpretation of a point estimate of adherence depends upon the study design and aims; was it an observational study or an RCT; or was the intervention comparing

two treatments or comparing an intervention to improve adherence to a control group. It is unusual for a study to report overall adherence of >80%[143] indicating that even in the context of a clinical trial adherence to maintenance ICS is imperfect. Severity of asthma, asthma symptoms or peak flow do not predict adherence[130,225]. There are two observational studies which present data from electronic inhaler monitors on ICS use in stable patients. One study, in adults with asthma or chronic obstructive pulmonary disease (COPD)[224], concluded that irregular use was common and only 20% of participants used their inhaler correctly and on time. The other study, in children with asthma[226], described four patterns of adherence to ICS; good adherence and improved asthma control; good adherence with poor asthma control; poor adherence with good asthma control and poor adherence with poor asthma control.

Associations between beta$_2$-agonist use and asthma outcomes was investigated by the SMART study[160], conducted in patients at risk of a sever exacerbation. Participants were randomised to budesonide-formoterol as maintenance and reliever therapy (SMART) or maintenance budesonide-formoterol with salbutamol reliever therapy and electronic inhaler monitors were attached to all the patients' inhalers. Data on beta$_2$-agonist use showed that budesonide-formoterol used as both maintenance and reliever (SMART group) resulted in fewer days of beta$_2$-agonist overuse[160]. In the maintenance budesonide-formoterol group, increasing use of salbutamol was a predictor of poor asthma control[152] and future adverse asthma outcomes including exacerbations[153,212].

Three observational studies present data on patterns of beta$_2$-agonist use in asthma. One study described two groups of participants; those who used SABA appropriately in response to symptoms (83% of participants); and those who used SABA erratically and inappropriately where SABA use was not correlated to symptoms (17% of participants)[192]. Another described six patterns of SABA use; either arbitrary under users, arbitrary appropriate users or arbitrary over users if SABA use was not associated with increased airway obstruction; or non-arbitrary under users, non-arbitrary appropriate users or non-arbitrary over users if SABA use was associated

with increased airway obstruction. Arbitrary use was more common than non-arbitrary use[227] indicating that use of SABA was related to other factors rather than just airway obstruction. A study in preschool children with asthma found SABAs were used on 63% of days when symptoms were documented, but use was variable and was not closely correlated with reported symptoms[228].

The literature on patterns of inhaler use shows adherence to maintenance ICS is often poor, higher use of SABA is associated with poor asthma outcomes and suggests that different patterns of SABA use exist which may not be related to airway obstruction. The SYGMA 1 and 2 and Novel START studies showed symptom-driven budesonide-formoterol lead to reduced exposure to ICS, however, there is limited data on frequency of ICS or beta$_2$-agonists are used, periods of no use and patterns of inhaler use.

1.4.2.2. Inhaler use during exacerbations and related to asthma severity

The authors of the SYGMA 1 and Novel START studies proposed that timing of ICS dose and increased use in response to symptoms may be more important than cumulative ICS exposure and be responsible for the equivalent or lower severe exacerbation rate between participants taking as-needed budesonide-formoterol and maintenance budesonide[176,178].

A study conducted in patients at risk of a severe asthma exacerbation, supports this theory as budesonide-formoterol given both as maintenance and reliever therapy reduced the risk of severe asthma exacerbations compared to high dose fluticasone-salmeterol maintenance therapy with SABA reliever therapy at approximately 60% of the dose of ICS[229]. In this study, episodes of high reliever use provided additional protection from exacerbations in those randomised to budesonide-formoterol maintenance and reliever therapy but not for those randomised to fluticasone-salmeterol maintenance with SABA reliever therapy. However, a drawback of this

study is the use of patient diaries to document inhaler use[229], therefore, the data is more susceptible to inaccuracies and bias.

The SMART study[160] provided detailed data on patterns of inhaler use around asthma exacerbations. The use of electronic inhaler monitors allowed the investigators to conduct post-hoc analyses at both the group and individual level on patterns of inhaler use prior to hospitalisation, or a severe exacerbations of asthma. Prior to hospitalisation for asthma[112] participants increased their use of beta$_2$-agonist use in the maintenance and reliever budesonide-formoterol arm and the maintenance budesonide with salbutamol reliever arm. However, there were differences in beta$_2$-agonist overuse between the treatment groups prior to hospitalisation. Those taking budesonide-formoterol reliever, used a median of 14 actuations of beta$_2$-agonist per day whereas for those taking salbutamol reliever it was 46 actuations per day. There was considerable variability in individual use of both ICS and beta$_2$-agonist in the 14 days prior to hospitalisation. Prior to either hospitalisation or a severe exacerbation[154], participants taking budesonide-formoterol reliever took more actuations of ICS than those taking salbutamol reliever, and cumulative dose of ICS was higher in those using budesonide-formoterol reliever therapy. Reliever use for participants using salbutamol was high for a longer period of time before and after a severe exacerbation than in those using budesonide-formoterol reliever therapy[154]. These post-hoc analyses suggest that use of budesonide-formoterol as reliever therapy is associated with different patterns of use to use of a SABA as reliever therapy, and leads to increased delivery of ICS during periods of worsening asthma.

Observational study data of inhaler use in connection with asthma exacerbations from electronic inhaler monitors showed, following discharged from hospital for an exacerbation of asthma, adherence to ICS fell to 50% within 7 days of discharge[157]. In this study population over 45% of patients had a history of near-fatal asthma, and those with a history of near fatal asthma were more likely to have poor adherence. Therefore, those most at risk of death from asthma were not taking their medications appropriately at a time they need them most. Another observational study in children found median adherence to ICS in those who had an exacerbation was 13.7%

compared to 68.2% in those that did not[194]. These studies suggest underuse of ICS around asthma exacerbations is a problem, which needs addressing. Use of symptom-driven budesonide-formoterol would increase use of ICS around exacerbations which could reduce the severity or even prevent exacerbations.

Through this section I have described why electronic inhaler monitors are the most appropriate method to accurately assess exposure to ICS and beta$_2$-agonists and explore patterns of inhaler use within an RCT. I have discussed the data from the SYGMA 1 and 2 and Novel START studies which suggests in mild asthma cumulative ICS exposure was not the primary determinant of risk of severe exacerbations. However, the mechanisms behind the findings from these studies is unclear and patterns of inhaler use are likely to help clarify how symptom-driven budesonide-formoterol has its clinical effects. Within the wider literature there is a paucity of data on patterns of ICS and beta$_2$-agonist use both during stable asthma and around asthma exacerbations. Detailed patient data on inhaler use will allow investigation of the hypothesis that timing and titration of ICS dose through the vehicle of a bronchodilator is more important than cumulative dose, which may explain why as-needed budesonide-formoterol has a similar or lower rate of asthma exacerbations compared to maintenance budesonide at significantly lower ICS exposure. This hypothesis will be investigated in Chapter 3 – the electronic monitoring sub-study.

Assuming that symptom-driven budesonide-formoterol is an effective alternative to maintenance ICS plus as-needed SABA in mild asthma, for it to be adopted into clinical practice patients would need to be willing to use this regimen. The final section of the Introduction will outline the literature on patient preferences for asthma treatment and how an as-needed budesonide-formoterol may align with what is known about patient preferences for treatment.

1.5. Patient preferences for asthma treatments

Introducing symptom-driven budesonide-formoterol to clinical practice would represent a paradigm shift in the management of mild-moderate asthma away from symptom-driven SABA monotherapy and daily maintenance ICS with SABA reliever therapy. Discussed in section 1.3.3 there is evidence that symptom-driven ICS-reliever regimens may be a safe and effective alternative in mild asthma. However, there is no data on the patient perspective on using symptom-driven budesonide-formoterol, which is necessary if it is to be incorporated into clinical practice. It would be counterproductive to introduce as-needed ICS-formoterol into asthma guidelines and clinical practice if it was unpopular with patients. This section will outline the literature on patient preferences for asthma treatment and how it may be relevant to patient preferences for symptom-driven budesonide-formoterol.

To understand methods for eliciting patient preferences for symptom-driven budesonide-formoterol, the theories and techniques for determining patient preferences will be summarised with a particular focus on discrete choice experiment (DCE) methodology. DCEs are relevant to this thesis because they allow strength of patient preferences for different aspects of asthma treatment to be determined. Knowledge on patient preference for asthma treatment obtained through DCEs will be systematically reviewed along with strengths and weaknesses of DCE methodology.

1.5.1. The literature on patient preferences for asthma treatment

Knowledge of patient preference for inhaler regimens can be extrapolated from data on their observed choices or behaviour, adherence, patterns of inhaler use and information on patients' necessity and concerns beliefs about medicines. Preferences determined from observed choices or behaviour are referred to as revealed preferences. Theories and models of determining preferences will be discussed in section 1.5.2.

Information on patients' revealed preferences for asthma treatments can be inferred by their patterns of use and adherence. Discussed in section 1.3.2, adherence to daily

maintenance ICS is often poor. Adherence to once daily regimens had been shown to be higher than adherence to twice daily regimens[207,209] and many patients have varying patterns of regular and irregular use of ICS inhalers[224,230]. This suggests that patients' revealed preference is not to take ICS inhalers twice a day. It is striking that adherence to regular ICS is poor even when the patient is faced with adverse asthma outcomes such as poor asthma control, high burden of symptoms, recent asthma exacerbations and even hospitalisation for asthma[91,95,96,128,157]. This provides evidence that patients prefer not to use their ICS inhalers even when experiencing adverse asthma events. Patients fill more prescriptions for reliever inhalers than preventer inhalers even though higher number of reliever inhalers obtained per year is associated with decreasing asthma control[128,208]. This indicates that patients' revealed preference is to use their reliever inhalers over the preventer inhalers.

Surveys on patient perceptions of their asthma[106,107,117,231] have found patients often underestimate their asthma, classing it as well controlled or mild, but admitting to regularly experiencing symptoms and exacerbations. In these surveys, reported use of SABA often exceeds that of ICS and many patients recognise worsening asthma and adjust their medication in response. However, they increase their use of SABA first, and only increase their use of ICS later and to a lesser extent[100]. Patients have reported they prefer to take more reliever medication than preventer medication for worsening asthma[119]. Because patients perceive their asthma as mild and symptoms are ameliorated with SABA they doubt the necessity of their regular ICS inhalers, which contributes to their preference for reliever inhalers over preventer inhalers[232]. Patients prefer treatments they can feel giving them immediate benefits[105] than ones which do not. Because taking ICS does not provide any noticeable immediate benefit, patients may perceive that they are not effective[233]. The episodic nature of asthma symptoms along with directions for use of SABA, can give patients the sense that they only need to take their medications for asthma intermittently when symptoms are troublesome[108,234]. Patients' expectations on the level of asthma control that can be

achieved is low. There is a gap in understanding between patients, physicians and recommendations set out in guidelines on what asthma control means, how it can be achieved, and the efficacy of taking preventer inhalers[99,115,231,235,236].

Use of inhalers is influenced by patients' perceptions on the necessity of their medications and their concerns about using them (the necessities and concerns framework as outline in Figure 6)[118,135,142,233]. A meta-synthesis of the qualitative literature on barriers to adherence in asthma[234] found key themes to be: the belief that asthma medications were not necessary or did not help; perception of only an intermittent need for medications; and medications were inconvenient to use. Many patients expressed a fear of side effects and wished to take as little medication as possible and reduce medication use when symptoms improve. Factor analysis of a survey in patients with asthma identified that adherence was significantly associated with perceived necessity, safety concerns, acceptance that asthma is a chronic disease and perception of medication effectiveness, ease of use and treatment regimen satisfaction[237]. A population based survey of 8,000 patients with asthma in Europe found the most common reasons for not taking a preventer inhaler every day as prescribed were not seeing the need to take it (50.0%) followed by forgetting (18.6%)[107]. This finding was replicated in a survey of 1,733 patients with asthma in the United States[236]. Another survey found increasing agreement with preventer inhalers being essential part of asthma therapy was significantly associated with adherence[119], and those with strong concerns over ICS are more likely to report low adherence[141,238].

Patients want asthma medications to effectively relieve symptoms quickly and to be long-lasting[100,239–242] but they have general and specific concerns about taking inhalers and their side effects so wish to limit the amount of medication they take[136,141,233,243]. Shortness of breath is one of the most significant symptoms to patients[107,241], symptom free days[243] and being able to carry out activities and sports without limitation from asthma are also important[239,240]. Cost of inhalers is a barrier to treatment [105,233,234,244], however, this may be country and healthcare system specific. Patients are more likely to adhere to and prefer regimens that are simple, easy to use and limit the number of different types of inhalers and inhaler devices[237,240,245,246].

They value convenience[243] and are more likely to choose and be adherent to a once a day preventer regimen over a twice a day regimen[139,207,234,247]. Patients express a desire to be in control of their asthma treatment[242], like to be able to adjust the amount of medication they take in response to their symptoms[239,240] and do not want regimens to be intrusive[139]. A study of patients with asthma in general practice revealed that 46% only took their ICS inhalers in response to symptoms and 13% took them regularly but at a lower than prescribed dose[166]. Patients have reported higher satisfaction with the SMART regimen than their previous asthma regimen and found the SMART regimen to be more effective, and easier to use with a lower burden of medication and side effects[248].

Therefore, symptom-driven budesonide-formoterol may align with patients' preferences to not to taken ICS every day, have a treatment that is flexible and convenient which they can titrate to their asthma symptoms, and provides fast relief. A symptom-driven budesonide-formoterol regimen is more consistent with these preferences than a maintenance budesonide plus as-needed terbutaline regimen. However, the literature also suggests that avoidance of shortness of breath and activity limitation is important to patients. The SYGMA 1 and 2 and Novel START studies found that asthma symptom scores were slightly higher in the as-needed budesonide-formoterol group than the maintenance budesonide group, so it is possible that an increase in symptom burden in return for a more flexible treatment regimen may not be a trade-off that patients are willing to make. Chapter 4 will aim to determine if patients have a preference for symptom-driven or maintenance ICS, and Chapter 5 will aim to quantify patient preferences for different aspects of symptom-driven and maintenance treatment.

1.5.2. Theories and methods of modelling patient preferences

Understanding the methods of determining patient preferences and the theories that underpin them is necessary to select the appropriate methodology for the question,

interpret results and understand the strengths and limitations of the data gathered. This is relevant to the third and fourth aims of this thesis; to determine if patients have a preference for symptom-driven or maintenance ICS, and to quantify their strength of preference for different aspects of asthma treatment. For example, if the question is "does someone prefer treatment A or B?", then a survey question presenting a dichotomous choice between A and B may be appropriate. However, questions such as "how does treatment X compare to previous a treatment?" or "what is the patient willing to trade off to get treatment X?" cannot be explored using dichotomous choices and alternative methodologies would be more appropriate.

Theories of how to determine patient preferences for treatments or services come from the fields of psychology and behavioural economics, where preferences of consumers are pivotal to modelling behaviour and market forces[249]. These theories have been extrapolated to health care where they are used to predict or model patient preferences for different treatments, screening programmes, vaccinations and services[250]. Data on consumer preferences can be divided into revealed preference data and stated preference data. Revealed preferences are based on the theory that a consumer's preferences can be revealed by observing their choices or behaviour. Revealed preference data are attractive because they are based on actual decisions (i.e. what a consumer did or purchased) so have high reliability and face validity[251]. However, revealed preferences can only ever be based on historical data and assumes that the consumer behaved rationally with full information of all alternatives and chose the product or service that provided them with the greatest utility, but this is not always the case[252]. This particularly applies to healthcare when patients may be faced with complex decisions between multiple options they don't fully understand or where a treatment may be decided by a health care provider with limited input from the patient. In addition, revealed preference data cannot exist for new medications or treatments[251].

Stated preference techniques are an alternative which have their theoretical origins in experimental economics, specifically in random utility theory[249]. Stated preferences is an umbrella term for a wide variety of instruments or surveys which allow choice or

preference to be estimated from a series of chosen and rejected alternatives[253]. Table 7 describes some of the different stated preference survey instruments. From the choices made, state preference techniques allow the preferences and priorities of the responder to be inferred[253]. An advantage of stated preference data is that it can allow preference for new or hypothetical products to be modelled. A product or service can be broken down into significant attributes for example price, brand, and distance to travel. This allows the influence of each attribute on preference and trade-offs to be determined[253], as a result, stated preference data allows a much wider range of preference behaviours to be modelled. However, a weakness of stated preferences data is that disparities may exist between the person's stated preferences and revealed preferences as there is often a behavioural gap between what people say they will do and what they actually do[254,255].

Table 7: Examples of stated preference survey instruments

Instrument	Explanation
Binary yes/no questions	Responders have a dichotomous choice to indicate if they would choose an option or not. This clearly delineates chosen and non-chosen options.
Rating scales/Likert scales	Responders indicate their preference or degree of agreement on a numerical scale. This provides information on order and magnitude of preferences.
Complete ranking of options	Options are ranked from most to least preferred which provides information on order of preference but no information on strength of preferences.
Willingness to pay	Willingness to pay for different options provides information on order, equality and differences in preference for the different options.
Discrete choice/ conjoint surveys	The responder chooses their preferred option between two or more differing profiles summarising attributes of a particular product or service.

Constructed from information provided in Stated Choice Methods: Analysis and Applications. Chapter 2: Introduction to stated preference models and methods page 20-22[253].

Within healthcare there are several methods for determining patients' preferences for different medications, regimens or services. In asthma, information on revealed preferences can be inferred from pharmacy dispensing data which can show if

patients are preferentially collecting one type of inhaler over another, particularly if compared to the patients' prescribed usage. Data from electronic inhaler monitors can provide information on patterns of inhaler usage and may provide further revealed preference data. Qualitative studies from one-on-one interviews or focus groups provides rich data on peoples' motivations, perceptions and feelings regarding their asthma treatment, however, as such data is usually only generated from a small sample of patients and it may not be generalisable to the wider population.

Stated preference techniques such as surveys where patients answer questions on their use of and preferences for asthma treatments can provide insights into the views and preferences of the wider population. An alternative approach to determine patients' preferences and priorities for asthma care is the use of DCEs which uses a mixture of qualitative and quantitative methodologies and can quantify patients' strength of preferences for multiple aspects of asthma care. In a DCE the area of interest (for example asthma treatment), is broken down into several attributes. Attributes can be any aspect of asthma treatment that is felt to influence patient preference or choice. Attributes are usually derived from qualitative studies into patient preference or priorities in the area that the DCE is investigating, along with review of the literature and expert opinion.

In a DCE survey, the participant is presented with a series of choice sets comprising of two or more profiles and asked to choose which profile they would prefer. Each profile contains the same attributes, however, the levels of the attribute differs between the profiles. An example choice set from a DCE investigating preference for asthma treatments is shown in Figure 8 and highlights the attributes used (number of symptom free days, dose, cost, thrush, tremors/palpitations, number of inhalers) and some of the levels of each attribute. DCEs assume that the participant makes choices based upon the utility they derive from each attribute in the profile and choose the option that provides them the highest utility thus indicating the importance of the attributes and, therefore, their preferences[251]. Through mathematical modelling, participant choices are used to determine their preferences for each attribute and level known as preference weights or part-worth utilities[256]. The preference weight of

an attribute or level indicates how much it influenced choice and therefore, patient preference for that particular attribute or level relative to all other attributes and levels. DCEs are being increasingly used in healthcare to assess patient preferences, value outcomes and trade-offs, develop services and allocate resources.

Question	**TREATMENT A**	**TREATMENT B**
Number of symptom free days (per month)	20	10
Dose (per day)	2	as-needed
Cost (per month)	$40	$20
Thrush (episodes per year)	1	3
Tremors/palpitations (episodes per month)	3 or more	2
Number of inhalers	1	2

Which treatment would you prefer (*check one box only*)?	Treatment A ❑	Treatment B ❑	Neither ❑

Figure 8: Example choice set from a DCE investigating preferences for asthma treatment[257]

1.5.2.1. Strengths and weaknesses of DCE methodology

To appreciate if use of DCE methodology was appropriate and interpret the results, an understanding of the unique strengths and weaknesses of DCE methodology is needed. Random utility theory underpins the psychological and economic theories of preferences and consumer behaviour that DCEs are derived from[258]. Random utility theory makes the following assumptions[256,258]:

i) The utility of a product or service in question can be broken down into separate components (attributes).

ii) People are rational decision makers and make choices that will maximise their personal utility or in accordance with their preferences.

iii) When presented with two or more choice alternatives, the utility assigned to each choice alternative depends on the attributes in the choice profiles.

iv) The choices or preferences of a person can be modelled mathematically. However, due to unknown or unmeasurable factors the full utility assigned by the choice maker to each of the alternatives cannot be known so this must be represented by a random variable in the model.

From the assumptions within random utility theory we can find potential weaknesses unique to DCE methodology, which can explain why preferences elicited by DCE may not always dovetail with revealed preferences or preferences elicited using other stated preference methods. While most products and services can be broken down into component attributes, if the chosen attributes do not significantly influence choice then the preference data from the DCE will have little meaning as the responders will be making random choices that they do not have a preference for[259]. Attribute dominance is another issue, where one attribute affects choice so significantly that all choices are made to maximise utility of it and choices made on all other attributes are random and do not reflect preference for those attributes[250,259].

Random utility theory assumes that people are rational decision makers, however, this is not always the case. This statement includes assumptions regarding what constitutes a rational choice, which may be subjective, or influenced by personal or cultural factors. While people may make rational decisions, they may be inconsistent in making choices that provide them with the greatest utility[260]. For example, from time to time people are likely to pick their second, third or even fourth favourite flavour of ice-cream. Or someone might make inconsistent choices based on the decision context or their level of engagement with the task[261].

A person's stated preferences (measured by a DCE) may differ from their revealed preferences (observed by their behaviour). When presenting a person with choice profiles within a DCE the profiles and choices the responder is making are always

hypothetical and the choices may not be influenced by the utility derived from the attributes in each choice profile[255,262]. This form of bias is described as hypothetical bias and can help explain discrepancies between choices made within the DCE and the choices that the person would make in reality. For example, we know from data on poor adherence and control in asthma that people are willing to accept more symptoms in order not to take their preventer inhalers regularly. However, DCEs exploring preferences for asthma treatment (reviewed in section 1.5.3) show that participants rated having few symptoms or well controlled asthma highly. This is probably because a choice profile can never truly reflect reality. In addition there is often a gap between what people say they are going to do and what they actually do[254,255]. Therefore, when a person is presented with two or more choice alternatives the utility assigned to each choice depends on more than is shown in the profiles[254].

This leads on to the assumption that the unknown or unmeasurable factors that influence preference and utility can be modelled using a random variable in the statistical model, if this is incorrectly modelled then the results from the DCE may be inaccurate[250,262].

Human factors such as inattention, boredom, lack of understanding or motivation to complete the task can lead to inaccurate data being gathered. In addition, cognitive burden and length of the survey can have a significant effect on the data quality, but can be avoided through appropriate pilot testing[263].

Many of the weaknesses of DCE methodology can be mitigated through appropriate design, testing and modelling[256,263,264]. In addition, stated preference data from DCEs can be combined in some cases with revealed preference data providing a fuller explanation of a target population's choices and preferences[262]. A systematic review and meta-analysis comparing the results of DCEs conducted in healthcare settings with choices made in reality concluded that DCEs can produce reasonably accurate predictions of health related behaviours[254,265].

Strengths of DCE methodology are they allow modelling of preference for medications or services that don't exist yet or for which there is no revealed preference data. This enables estimation of the uptake of a new medication or service[253]. In addition, as well as measuring the influence of positive effects on preference they can measure negative effects on preference[260]. They are adaptable, can be used in a wide variety of settings and with different groups of people and can be used to gather data from a large of number of people quickly. For example, they have been used effectively to determine preference for breast screening in women from Malawi[266], and to determine preferences for payment for asthma medication from over 1,000 patients in Australia[267].

While any method is subject to weaknesses and biases, DCEs are a useful tool to determine preferences for existing and hypothetical treatments. They provide data on whether an attribute is important and how important it is in relation to the other attributes. This allows strength of preference for multiple aspects of a treatment regimen to simultaneously be determined through the choices and trade-offs that the person answering the survey makes.

These qualities of DCE methodology will enable the strength of patients' preference for symptom-driven budesonide-formoterol or maintenance budesonide plus terbutaline as needed to be determined along with the importance of treatment regimen relative to other aspects of asthma management. Relating data on strength of patient preferences for different aspects of asthma treatment to measured properties of both symptom-driven and maintenance regimens could be used to determine which regimen may be appropriate for patients based on their preferences and treatment priorities. The evidence from DCEs investigating patient preferences for asthma treatments will be reviewed next to determine what is already known from DCEs on patient preferences and priorities for asthma management.

1.5.3. Systematic review of discrete choice experiments in asthma

To identify DCEs investigating patient preferences for asthma management Ovid was used to search Embase (1947-present), Medline (1948-present), Scopus and ECONLIT on 12th November 2018 using the following search strategy:

- 'discrete choice experiment', OR 'discrete choice analysis', OR 'discrete choice modelling', OR 'discrete choice', OR 'DCE', OR 'conjoint analysis', OR 'conjoint', OR 'stated preference', OR 'part-worth utilities', OR 'best worst', OR 'maximum difference scaling', OR 'maxdiff', OR 'max diff'
- AND 'asthma' OR 'asthmatic' OR 'airways disease'

Results were limited to English language, titles and abstracts were screened and full texts of potentially relevant papers were obtained.

The results of the search strategy are shown in Figure 9.

Studies that used DCE methodology to investigate patient preferences for medications, symptoms of asthma or aspects of disease control were included. A summary of studies is provided in Table 8.

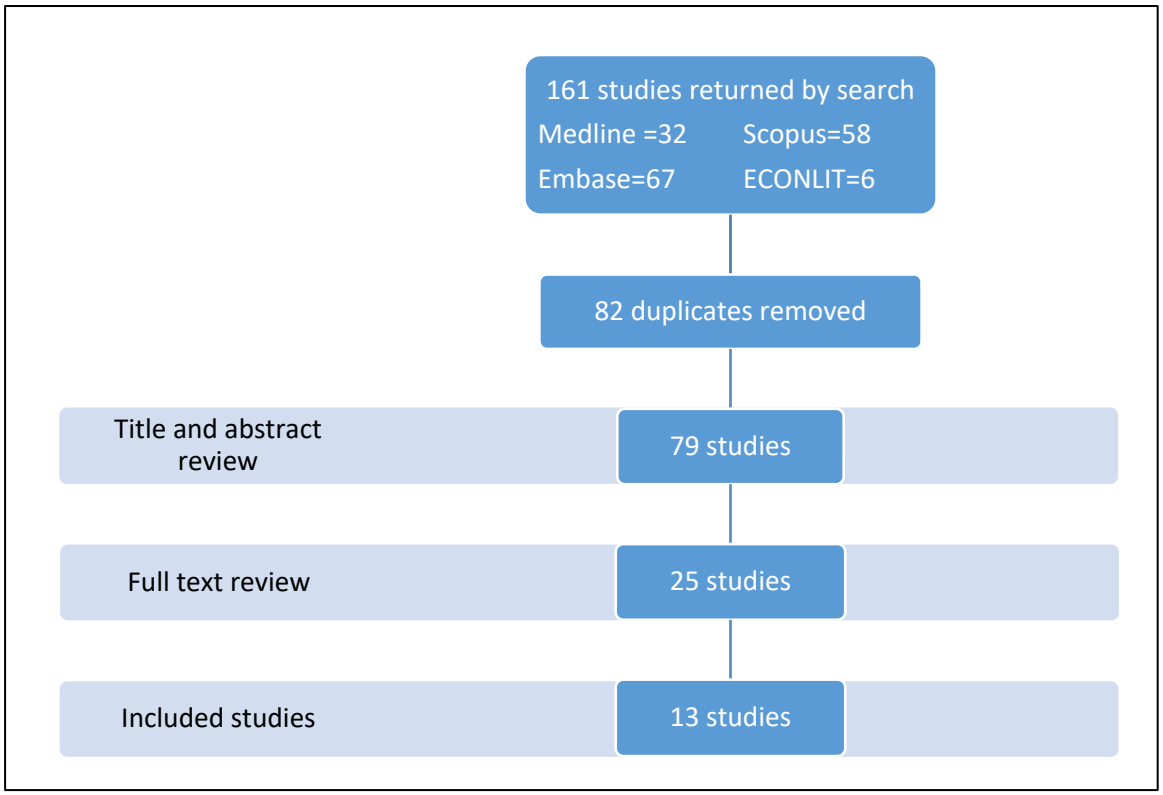

Figure 9: PRISMA diagram for systematic review of DCEs in asthma

Table 8: Systematic review of DCEs in asthma

Paper	Objective	Sample size	Participants	Key findings	Limitations
Hauber 2009[268]	Quantify the importance of speed of onset for combination ICS/LABA maintenance medication	509	Members of an internet survey panel who self-reported a diagnosis of asthma and were using ICS/LABA	• Satisfaction with how quickly medication began to work was the most important attribute to patients • Second was being able to tell the medication was working and third was being able to feel the medication begin to work right away • The least important attribute was feeling physical sensations shortly after taking the medication that reassured the patient it was working	Used a pre-existing questionnaire for the attributes, comparing current treatment with a hypothetical one
Haughney 2007[269]	Quantify relative importance of features of asthma management from the patient's perspective	148	Patients at selected GP surgeries on Step 3 treatment or above according to British asthma guidelines	• Number of inhalers was the most important attribute with patients preferring regimens with fewer inhalers • Steroid dose was the second most important attribute with patients preferring regimens with lower steroid dose • Use of a personal asthma plan was the third most important attribute • Surprisingly controlling asthma symptoms was the least important attribute to patients • Authors conclude that adults with moderate-severe asthma would trade improvements in symptom relief for a simpler regimen with fewer inhalers	Participants all came from selected GP surgeries which may affect generalisability, some levels unrealistic and may be vulnerable to hypothetical bias
Hitchcock 2007[270]	Assess caregivers preference for different attributes of their child's asthma treatment	186	Caregivers of children aged 1 to 4 years with asthma	• Caregivers preferred treatments that required minimal effort and co-ordination on the child's part, were approved by the US Food and Drug Administration in children as young as 12 months, took less time to administer, had flexible dosing and were easily portable were preferred by caregivers	Relevance of some attributes may be limited outside USA

Paper	Objective	Sample size	Participants	Key findings	Limitations
*King 2007[271]	Assess patient preferences for preventer medications	52	Patients part way through participating in a randomised clinical trial looking at outcomes using 3 different preventer medications	• When presented with the option of continuing with their current medication or taking the new hypothetical medication presented most patients opted to continue with their current medication • Being able to participate in sports and usual daily activities were the most significant attributes • Symptom control was only significant at the lowest level – having minimal symptoms • Participants were significantly less likely to choose the option with side effects • Cost significantly affected choice but other convenience attributes such as frequency of collecting prescriptions, dosing frequency and need for peak flow monitoring were not significant	Comparing current treatment to a hypothetical one, small sample size, participants in an RCT may not be representative, likely affected by hypothetical bias
Laba 2019[267]	To investigate if a financial incentive in the form of a reduced co-payment for ICS increased the uptake of controller medications	1401	Adults and children with asthma from an internet panel	• Preference for inhaler decreased with increasing costs to the patient or government, and increasing chance of a repeat visit to the doctor • Preference across all groups was for fewer symptoms • Adults preferred high strength inhalers but parents of children preferred low strength inhalers • The DCE predicted higher levels of patients choosing treatment with ICS than was actually prescribed • Patient directed financial incentives are unlikely to encourage much switching of medications and current under treatment with ICS was not explained by patient preferences	Did not model adherence, some participants may not have been appropriately diagnosed. Focus of study was on cost of medications rather than preferences for management

Paper	Objective	Sample size	Participants	Key findings	Limitations
*Lancsar 2007[272]	Explore patient preference in relation their current preventer, a hypothetical preventer or no preventer	57	Patients starting a randomised clinical trial looking at outcomes using 3 different preventer medications	• Participants had a strong preference for their current medication • Being able to participate in sports and strenuous activities had the strongest influence on choice. • Having no restrictions on normal activity, no night waking, no side effects and never having to monitor peak flow consistently affected choice • Attributes associated with convenience such as frequency of collecting prescriptions, dosing frequency, route of administration (tablet vs inhaler) did not significantly affect choice • Strength of doctor's recommendation also did not affect choice	Comparing current treatment hypothetical one, small sample size, participants in an RCT may not be representative
Lloyd 2007[273]	Capture patient preferences for different aspects of asthma treatment	479	Adults with asthma in UK, Netherlands and Spain	• Participants were willing to pay the highest amounts to avoid asthma attacks that required emergency care • They were willing to pay the second highest amount to avoid days with asthma symptoms • Willingness to pay to avoid a self-managed asthma attack was higher than willingness to pay to reduce days needing reliever inhalers or risk of side effects • They were not willing to pay much to avoid common mild side effects	Different drug payment systems between 3 countries affects willingness to pay
McKenzie 2001[274]	Determine relative importance of different asthma symptoms	162	Patients with moderate to severe asthma	• Patients weighted some symptoms more highly than others • Cough and breathlessness were the most important attributes • Wheeze, chest tightness and sleep disturbance were also significant	Only asked moderate-severe asthma population may not be generalisable to mild asthma

Paper	Objective	Sample size	Participants	Key findings	Limitations
McTaggart-Cowan 2008[257]	Quantify treatment preferences	157	Adults with asthma	• Patients preferred treatments that gave them more symptom free days but were willing to trade days without symptoms for reduction in exacerbations and side effects and for greater convenience such as reduced number of doses per day and only one inhaler • The preference for taking a medication once a day compared to as needed was not significant	High prevalence of neither response, generalisability of results outside study population
Osman 2001[275]	Assess the relative importance of different asthma symptoms	272	Adults attending specialist asthma clinics	• Patients were more likely to choose scenarios with low levels of cough and breathlessness than scenarios with low levels of sleep disturbance, wheeze or chest tightness	Uncertain if sample representative and results generalisable
Svedsater 2017[276]	Investigate patient preferences for treatment factors	152 (150 patients with COPD also did the DCE, but their results are not discussed)	Adults with asthma	• Having well controlled symptoms was the most important attribute • Other preferred attributes were for no sleep disturbance and low cost of medication • Preferences for easy/convenient use, no exacerbations, low medication frequency and a treatment that enabled desired social and physical activity were also significant	Large number of attributes so high cognitive burden on participant, possible selection bias, no additional data on preferences
¥Walzer 2007 [277,278]	Investigate caregivers preference for asthma medication in preschool children	42	Caregivers of preschool children with asthma	• Episode free days was the most important attribute • Out of pocket expense was the second most important attribute • Exacerbation risk was the least important attribute	Limited data on how study was conducted, questions over rigor, reported findings across two separate manuscripts

*Both studies were conducted at different time points within the same RCT

¥Author presented the same data set in two manuscripts, with a slightly different focus

1.5.3.1. Summary of findings from the systematic review of DCEs in asthma

1.5.3.1.1. Asthma symptoms and exacerbations

Ten of the 13 DCEs in this systematic review included attributes for specific asthma symptoms or the prevalence of asthma symptoms and four of the 13 DCEs included attributes related to asthma exacerbations.

Osman et al.[275] and McKenzie et al.[274] conducted DCEs with the aim of determining the importance of different asthma symptoms to patients. Osman et al. found preference weights for cough and breathlessness were twice that of chest tightness, wheeze and sleep disturbance. Patients were most likely to choose profiles with low levels of breathlessness and cough[275]. The findings from McKenzie et al. were similar to those of Osman et al. They found that all asthma symptoms included significantly affected preference with some symptoms affecting preference more strongly than others. Daytime cough and daytime breathlessness were more important symptoms to patients than daytime wheeze, chest tightness or sleep disturbance[274].

King et al.[271] and Lancsar et al.[272] conducted two DCEs in the same sample of participants, at the start of a RCT into controller medications for asthma and then part way through the trial. Both studies found participants preferred treatments that led to minimal asthma symptoms, allowed them to participate in strenuous activity and have no restrictions on their usual activities. Waking at night, chest tightness and cough also affected preference but not as strongly. Svedsater et al.[276] found having well controlled symptoms was the most significant attribute. Laba et al.[267], Lloyd et al.[273], McTaggart et al.[257] and Walzer et al.[277,278] all included attributes relating to symptom frequency and found that participants had a significant preference for the lowest frequency of symptoms or increasing the number of symptom free days. McTaggart et al.[257] found overall participants preferred symptom free days, however, they were willing to trade symptom free days for a reduction in exacerbations, side effects or for more convenient treatment regimens.

In contrast, Haughney et al.[269] found controlling asthma symptoms was the least significant attribute in a DCE investigating the importance of different features of asthma management. They suggested that this might be because the participants were willing to trade off symptom control for other features of asthma management. However, this attribute was presented as whether asthma symptoms were controlled by the patient changing their own therapy in response to symptoms or if they spoke to a doctor or nurse before making changes, so this attribute did not represent the prevalence or burden of symptoms in the same way as the other DCEs did.

Haughey et al.[269], Lloyd et al.[273], Svedsater et al.[276] and Walzer et al.[277,278] all included an attribute that related to asthma exacerbations. Lloyd et al.[273] found that participants were willing to pay the highest amount (€109.48) to avoid asthma attacks that required an emergency trip to a doctor or the emergency department and the third highest amount (€15.74) to avoid asthma attacks that did not require emergency medical attention. Svedsater et al.[276] found that frequency of exacerbations/flare-ups significantly influenced preference, however, this was the fourth most important attribute after sleep disturbance, cost and ease of inhaler use. Haughney et al.[269] found that asthma crisis management was the fourth most important attribute with participants preferring to avoid attending hospital. Asthma crisis management was less important than treatment specific attributes but more important than symptom control. In the DCE undertaken by Walzer et al.[277,278] exacerbation risk was the least important attribute.

1.5.3.1.2. Medication and regimen preferences

Ten of the 13 DCEs included attributes on participants' preferences for reliever and preventer medications or their asthma regimens. Two DCEs included attributes specific to reliever medications. Haughney et al.[269] found participants valued change in symptom relief provided by the reliever inhaler from mostly to completely. Lloyd et al.[273] found number of days you needed to use a reliever per week was the second least important attribute. This suggests that patients do not mind needing to use their reliever inhalers but want them to provide complete relief when they do.

Eight of the 13 DCEs included attributes specific to preventer medications. King et al.[271] and Lancsar et al.[272] found that route of administration either as an inhaler or tablet did not significantly affect choice. Haughney et al.[269] found patients preferred to have a lower dose of their preventer inhaler which could be increased as needed rather than a high dose all the time. Whereas Laba et al.[267] found that adults preferred higher strength inhalers but the parents of children preferred lower strength inhalers, however, inhaler strength was less important than symptom burden. Hitchcock et al.[270] and Walzer et al.[277,278] found in parents of children in the USA, FDA approval of preventer medication was the most significant determinant on preference and Hitchcock et al. found that consistency of dose delivery was the second highest influence on choice. King et al.[271] and Lancsar et al.[272] found strength of a doctor's recommendation was not a significant determinant of choice.

Hauber et al.[268] conducted a DCE on patient satisfaction with their combination ICS-LABA inhalers. They found that how quickly the medication began to work was the most important attribute, the second was being able to tell the medication was working and the third being able to feel the medication working right away. The least important attributes were feeling physical sensations to reassure that it was working and the preventer medication worked as quickly as the patient's reliever medication. However, the questions asked by this DCE are problematic as many ICS-LABA containing inhalers are taken as preventers so patients would not expect to gain immediate relief. In addition, salmeterol (a LABA) used in some ICS-LABA inhalers has a speed of onset time of over 30 minutes[51].

Four DCEs included a side effects attribute. Lloyd et al.[273] included mild side effects as an attribute and found that patients were not as concerned about avoiding mild side effects as they were about the other attributes. However, they limited the attribute to mild side effects and did not include more severe side effects in their DCE. McTaggart et al.[257] found that patients were willing to forgo some symptom free days for a lower risk of side effects. King et al.[271] and Lancsar et al.[272] found that while occurrence of side effects significantly affect choice, occasional hoarse speech was less likely to affect choice than tremors, palpitations, headache or oral thrush.

Nine DCEs included attributes related to regimen convenience. Haughney et al.[269] found that the number of different inhalers was the most important attribute with participants strongly favouring having fewer different types of inhaler; Lloyd et al.[273] found the number of preventer inhalers was almost equal to asthma attacks in influencing preference and McTaggart et al.[257] found that participants had a strong preference for having one inhaler over two or three. Hitchcock et al.[270] found flexible dosing schedule was the second least important determinant of preference. However, the attribute only contained two levels; fixed dose twice a day; or flexible dosing once or twice a day. So participants may not have interpreted the levels as being sufficiently different for them to affect choice. McTaggart et al.[257] found participants were willing to forgo some symptom free days for a reduction in frequency of medication administration. Svedsater et al.[276] found medication frequency was the fifth most important attribute and ease of inhaler use and convenience was the sixth. King et al.[271] and Lancsar et al.[272] found attributes relating to convenience such as frequency of taking the medication or frequency of collecting the prescription did not significantly affect choice, however, not needing to monitor peak flow was a significant determinant of choice. Laba et al.[267] found that preference decreased as the chance of having to visit the doctor again to change medication increased.

Six DCEs included cost as an attribute. King et al.[271] and Lancsar et al.[272] found increasing cost significantly influenced participant preference; Walzer et al.[277,278] found cost was the second most important attribute; and McTaggart et al.[257] found that participants preferred treatments that cost less. In contrast, Svedsater et al.[276] found that cost was the least important attribute. However, they conducted their DCE in the UK where patients pay a fixed charge for prescriptions and many patients get their prescriptions for free. This may have made the participants less sensitive to cost of the medication.

1.5.3.1.3. Conclusions

DCEs conducted in patients with asthma found presence of asthma symptoms or risk of exacerbations significantly affect patient preferences. However, the degree to

which asthma symptoms and exacerbations influenced patient preference varied between studies. Breathlessness and cough had a greater impact than wheeze, night waking or chest tightness. Being able to undertake physical activities and activities of daily living without being restricted by asthma was important. Patients would rather have as few symptoms as possible, however, they may be willing to trade off symptom frequency for other attributes such as attributes representing convenience. It is clear that presence of asthma symptoms is one of the most important determinants of preference to patients. How this data relates to symptom-driven budesonide-formoterol is unclear as the SYGMA 1 and 2 studies and Novel START studies found patients had higher symptom scores than those taking maintenance budesonide. However, the difference between the groups was mild and there is evidence from previous DCEs that patients may be willing accept a small increase in symptoms for a more flexible regimen.

Overall, asthma exacerbations were a significant predictor of patient preference. If, as suggested by the Novel START study the rate of severe asthma exacerbations is lower with symptom-driven budesonide-formoterol then this regimen may be more appropriate for patients with mild asthma who have a preference to avoid asthma exacerbations. Some of the heterogeneity between studies may be explained by the wording used in the attribute, which highlights the importance of how attributes and levels are presented in a DCE and the difficulties in comparing results between studies. For example, Haughney et al. and Lloyd et al. presented the exacerbation attribute as how the exacerbation would be managed (for example by attending hospital or self-managing). Svedsater et al. described it as frequency of exacerbations per year and Walzer et al. described it as percentage of patients who would experience a mild to severe exacerbation per year.

With respect to preferences for medications and treatment regimens, the literature suggests that patients prefer reliever medications which completely relieve symptoms but don't mind how many times a week they need to use it. Therefore, patients using symptom-driven budesonide-formoterol may not object to using a reliever medication more frequently than if they were taking maintenance budesonide (assuming they

were adherent). There is conflicting evidence on how strength of ICS in the inhaler affects preference. The influence of side effects on preference again may be affected by how the attribute is presented. For example, if the attribute refers to mild side effects or individual specific side effects. Cost is likely to influence choice however this might be country or healthcare system specific. Attributes of regimen convenience show that participants favour having fewer inhalers, which is supportive of symptom-driven budesonide-formoterol because with this regimen patients only have one type of inhaler. However, the literature suggest that patients may be more ambivalent about other aspects of regimen convenience such as frequency of preventer use, but this is at odds with the data on patients' adherence to preventer inhalers and may be related to how frequency of dosing attributes were presented, or hypothetical bias.

1.6. Introduction summary

Throughout the Introduction I have described why mild-moderate asthma is a significant clinical problem with a high symptom burden, risk of exacerbations and associated morbidity. Much of which is directly related to poor adherence to daily preventer inhalers. Therefore, a new treatment paradigm is needed. I have presented evidence for symptom-driven budesonide-formoterol as an alternative in mild-moderate asthma. I have discussed how patterns of inhaler use may be more important than cumulative dosing in preventing severe asthma exacerbations and how patterns of inhaler use can be determined in the setting of a RCT. Finally, I have discussed the literature on patient preferences for asthma treatments including data on revealed and stated preferences, with a focus on patient preferences obtained through DCEs, and discussed the evidence that taking symptom-driven budesonide-formoterol may be an acceptable management strategy to patients.

The following four chapters will address the four aims specified in the Thesis Aim:

1. The PRACTICAL study (chapter 2), a RCT that will investigate if symptom-driven budesonide-formoterol is an effective and safe alternative to maintenance budesonide with as-needed terbutaline in patients with mild-moderate asthma.

2. The electronic monitoring sub-study (chapter 3) will explore exposure to ICS and beta$_2$-agonists and patterns of ICS and beta$_2$-agonist use during the PRACTICAL study.

3. The preferences survey (chapter 4) will determine patient preferences for the treatment regimens used in the PRACTICAL study and their preferences for, satisfaction with and beliefs about the preventer and reliever inhalers.

4. The discrete choice experiment (chapter 5) will quantify the strength of patient preferences for different aspects of the asthma regimens used in the PRACTICAL study.

2. The PRACTICAL Study

2.1. Introduction

The PRACTICAL study was designed to extend and complement the findings of the SYGMA 1 and 2 and Novel START studies by comparing the efficacy and safety of symptom-driven budesonide-formoterol with maintenance budesonide plus terbutaline as needed in patients with mild-moderate asthma in an open label clinical trial, designed to be close to real world practice. The real world, open label design and inclusion of patients with moderate asthma means the results will be generalisable to a wider range of patients in the community with mild-moderate asthma and the benefits of using a single inhaler in the symptom-driven budesonide-formoterol group will not be lost. The PRACTICAL study will address the first aim of this thesis which was to compare the efficacy and safety of symptom-driven budesonide-formoterol with twice daily maintenance budesonide plus terbutaline as needed.

This chapter will describe the aim, methods, results and conclusions of the PRACTICAL study. The subsequent chapters describe three sub-studies which were nested within the main PRACTICAL study; the electronic monitoring sub-study, the preferences survey and the discrete choice experiment. The PRACTICAL study was published in The Lancet in August 2019[279]. As an author of the published article I retain the right to include it in a thesis or dissertation, provided it is not published commercially. Permission is not required.

2.2. Aim

The aim of the PRACTICAL study was to compare the efficacy and safety of as-needed budesonide-formoterol with maintenance budesonide plus as-needed terbutaline.

2.3. Methods

2.3.1. Study design

The PRACTICAL study was a "real world design", 52-week, open label, parallel group, multicentre, phase III, RCT conducted at 15 sites across New Zealand. The intention of the "real world design", broad inclusion criteria and limited study interventions was so patient selection and behaviour would better reflect what happens during routine clinical practice[179]. For this reason, the study was not blinded and no placebo inhalers were used and the broad inclusion criteria aimed to increase the generalisability of the results to a wider range of patients with a diagnosis of mild-moderate asthma. The study protocol has been published[280]. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Ethical approval was granted by Northern B Health and Disability Ethics Committee (15/NTB/178) (approval is located in Appendix 8.1). The study was independently funded by a grant from the Health Research Council.

2.3.2. Participants

890 adults aged 18-75 with a self-reported diagnosis of asthma were recruited from 15 sites across New Zealand. Sites were a combination of General Practitioner (GP) practices and clinical trials units. Participants were using SABA for relief of asthma symptoms with or without low-moderate dose ICS. The inclusion and exclusion criteria are given in Table 9. All participants provided written informed consent and a copy of the participant information and consent sheet is provided in Appendix 8.2.

Table 9: PRACTICAL study inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Adults aged 18–75 years	Self-reported past admission to the intensive care unit with life threatening asthma
Self-report of a doctor's diagnosis of asthma	A home supply of prednisone for use in worsening asthma, as part of a current asthma plan
Not used ICS in the 12 weeks prior to entry into the study and: - Asthma symptoms or need for SABA ≥2 occasions in the last 4 weeks, or - Waking due to asthma ≥ once in the last 4 weeks, or - Exacerbation requiring oral corticosteroids in the last 52 weeks	Self-reported treatment with oral prednisone or other systemic corticosteroids in the 6 weeks before potential study entry (representing recent unstable asthma)
Used ICS in the 12 weeks prior to entry in the study, and prescribed ICS at low or moderate doses (≤500 µg/ day fluticasone propionate or small particle formulation beclomethasone dipropionate (Qvar); ≤800 µg/day budesonide; ≤1000 µg/day beclomethasone dipropionate (Beclazone)), and: - Has partly or well-controlled asthma as defined by GINA guidelines, or - Has uncontrolled asthma as defined by GINA guidelines and either poor adherence to ICS and/or unsatisfactory inhaler technique	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 corticosteroids were permitted
Willing and able to give informed consent	Self-reported diagnosis of chronic obstructive pulmonary disease, bronchiectasis or interstitial lung disease
Able and willing to comply with all trial requirements	Self-reported ≥ 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
Willing to allow their general practitioner to be notified of participation in the trial	Current or planned pregnancy or breast feeding within the study period
	Other illnesses likely to compromise participant safety or impact on the feasibility of results Unwilling or unable to switch from current asthma treatment regimen

2.3.3. Randomisation and blinding

Patients were randomly assigned with a ratio of 1:1 to either symptom-driven budesonide-formoterol or maintenance budesonide plus terbutaline in response to symptoms. The randomisation sequence was generated by the study statistician and was concealed from the study investigators and participants through the electronic case report form. Randomisation was stratified by site and by baseline ICS use with a block size of eight. Neither investigators nor patients were blinded to their treatment allocation. The study statistician was blinded for analysis of the primary outcome variable.

2.3.4. Study interventions and procedures

The two treatment arms in the PRACTICAL study were:

1. Budesonide/formoterol 200/6µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as needed for relief of symptoms.
2. Budesonide 200µg (Pulmicort Turbuhaler, AstraZeneca) one inhalation twice daily plus terbutaline 250µg (Bricanyl Turbuhaler, AstraZeneca) two inhalations as needed for relief of symptoms.

Participants were provided with a written asthma plan specific to their randomised treatment arm (supplied in Appendix 8.3), education on their asthma plan and were taught how to use their inhalers. All patients remained under the care of their usual healthcare providers for the duration of the trial. Patients attended for six study visits over 52 weeks at week 0 (randomisation), 4, 16, 28, 40 and 52. The schedule of study visits and investigations is provided in Table 10. On treatment FEV_1[281] and FeNO was measured at randomisation and week 16 and 52. At every study visit patients filled out the ACQ-5[180], provided information on asthma exacerbations, systemic corticosteroid use, healthcare utilisation for asthma, adverse events, and were reminded of their asthma plan and correct inhaler technique.

Table 10: Schedule of study visits

Visit Number	**Consent & Enrolment**	**1**	**2**	**3**	**4**	**5**	**6**
Week	≤0	0	4	16	28	40	52
Written informed consent	X						
Inclusion/Exclusion criteria check	X	X					
ACQ-5		X	X	X	X	X	X
Participant preferences survey and discrete choice experiment*							X
Medical history & demographics		X					
Weight & height		X					
FeNO		X		X			X
Spirometry		X		X			X
Blood test for full blood count		X					
Randomisation		X					
Study ICS inhaler technique assessment			X	X	X	X	X
Participant education & issuing of study inhalers		X	X	X	X	X	
Issue written asthma action plan and other written information		X					
Inform GP of study enrolment		X					
Review: - Exacerbations - AEs¥ - SAEs± - Medication changes			X	X	X	X	X
If participant is to be withdrawn, documentation of cause and notification to GP and Sponsor			X	X	X	X	X
Inform GP and Sponsor of study completion							X

*completed by a subgroup of participants at selected sites.
¥AE – adverse event
±SAE – serious adverse event

2.3.5. Data safety and monitoring

A data safety monitoring committee was established, independent from the study team who reviewed all serious adverse events and were responsible for reviewing the interim safety analysis, which was conducted after 500 patients had been randomised. The proportions of participants with an unplanned hospitalisation for asthma was compared with the expected proportion of 2%. At the interim safety analysis no participants had been hospitalised for asthma, so it was not necessary to undertake a safety review of the study. A clinical trials monitor was responsible for monitoring the

study and an electronic case report form was used for data entry for each participant. All asthma exacerbations and severe adverse events were verified by three people, 10% of all other data points were independently monitored.

2.3.6. Outcomes

The primary outcome was the rate of severe asthma exacerbation per patient per year. Severe exacerbations were defined according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria of; either the use of systemic corticosteroids for three or more days for asthma; hospitalisation or emergency department visit for asthma with use of systemic corticosteroids for any duration[281].

Key secondary outcomes are given in Table 11.

Table 11: PRACTICAL study key secondary outcomes

Secondary outcomes
Rate of moderate and severe asthma exacerbations per patient per year. A moderate asthma exacerbation was defined as worsening of asthma leading to unplanned medical review; or worsening of asthma leading to the use of systemic corticosteroids for any duration
Time to first severe exacerbation
Time to first moderate or severe asthma exacerbation
Proportion of patients withdrawn due to treatment failure. Treatment failure was defined as either increase in asthma treatment for 14 days or more by the patient's usual healthcare provider or uncontrolled asthma leading to safety concerns
ACQ-5 score[180]
On treatment FEV_1[281]
FeNO
Adverse events and serious adverse events

2.3.7. Sample size calculation

The primary outcome variable was the rate of severe exacerbations per patient per year. Assuming a dropout 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

of 5%, to detect a 38% reduction in the rate of severe exacerbations of 0.62 representing a reduction from 0.30 to 0.185 per patient per year.

2.3.8. Statistical analysis

Mean and standard deviation (SD) and median and interquartile range (IQR) are presented for continuous variables. Categorical variables are described by counts and proportions expressed as percentages.

The statistical analysis was an intention-to-treat superiority analysis. The primary analysis was comparison of the rate of severe exacerbations per patient per year by Poisson regression with an offset for the number of days in study. No adjustment for over-dispersion was necessary because the degree of freedom was close to the deviance indicating that over dispersion was unlikely to be a problem. Analysis for the rate of moderate and severe exacerbations was also by Poisson regression with an offset for the number of days in study.

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, baseline ICS use, baseline SABA use (in previous 4 weeks), baseline FeNO and baseline blood eosinophil count.

Survival analysis with Kaplan-Meier plots and Cox proportional hazards regression was used to calculate the hazard ratio for 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 Hodges-Lehmann estimate of location difference were 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. SAS version 9.4 (SAS Institute Inc., Cary, USA) was used for all analyses.

2.4. Results

890 participants were randomised between 04/05/2016 and 22/12/2017. Five ineligible participants were randomised in error so the intention to treat data set included 885 participants. 437 participants were randomised to as-needed budesonide-formoterol and 448 to maintenance budesonide plus terbutaline as needed. The baseline demographics of participants in both treatment arms is given in Table 12. The flow of the participants through the trial is given in the Consolidated Standards of Reporting Trials (CONSORT) diagram in Figure 10. Participants in both treatment arms were similar with respect to baseline demographics. At study entry 621 of 885 participants (70%) had taken ICS in the preceding 12 weeks, overall mean self-reported adherence to ICS was 57% of prescribed dose. 204 of 885 participants (23%) had well controlled asthma and 681 (77%) had partly or uncontrolled asthma as defined by the GINA symptom score[282]. 12% reported a severe asthma exacerbation in the preceding 12 months.

Table 12: Baseline demographics of participants in the PRACTICAL study

Characteristic	Budesonide-formoterol as needed (n=437)	Maintenance budesonide plus terbutaline as needed (n=448)
Age (years)	43.3 (15.2)	42.8 (16.7)
Age at diagnosis (years)	19.5 (17.7)	18.8 (18.1)
Sex no.(%)		
Female	244 (56%)	241 (54%)
Male	193 (44%)	207 (46%)
Ethnic origin no.(%)		
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 no.(%)		
Current	39 (9%)	24 (5%)
Ex-smoker	123 (28%)	112 (25%)
Never	275 (63%)	312 (70%)
Pack-years (ever smokers)	4.5 (4.7)	4.6 (4.7)
Use of ICS at randomisation* no.(%)	305 (70%)	316 (71%)
Adherence to ICS (% of prescribed dose)¥	54.8% (37.0; n=304)	58.6% (47.3; n=315)
Use of ICS ever no.(%)	390 (89%)	381 (85%)
Weekly occasions of SABA use		
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 admission for asthma ever (number per patient)	0.7 (5.1)	0.5 (2.1)
Severe exacerbation in previous 12 months no.(%)	53 (12%)	52 (12%)
ACQ-5 score†	1.1 (0.8)	1.2 (0.8)
GINA symptom control no.(%)		
Well controlled	101 (23%)	103 (23%)
Partly controlled	209 (48%)	226 (51%)
Uncontrolled	127 (29%)	119 (27%)
On treatment FEV_1 (% of predicted)	87.8% (16.4)	87.4% (16.3)
FeNO (ppb)	26.0 (15.0–51.0)	30.0 (18.0–62.5)
Blood eosinophil count (x10^9 per L)	0.3 (0.2)	0.3 (0.2)

Values are expressed as means (SD) or median (IQR) unless otherwise indicated

* Participants self-reported ICS use in the 12 weeks prior to randomisation

¥ Participant self-reported adherence to ICS in the 4 weeks prior to enrolment (% prescribed dose).

† The Asthma Control Questionnaire–5 (ACQ-5) consists of five questions that assess asthma symptoms in the previous week

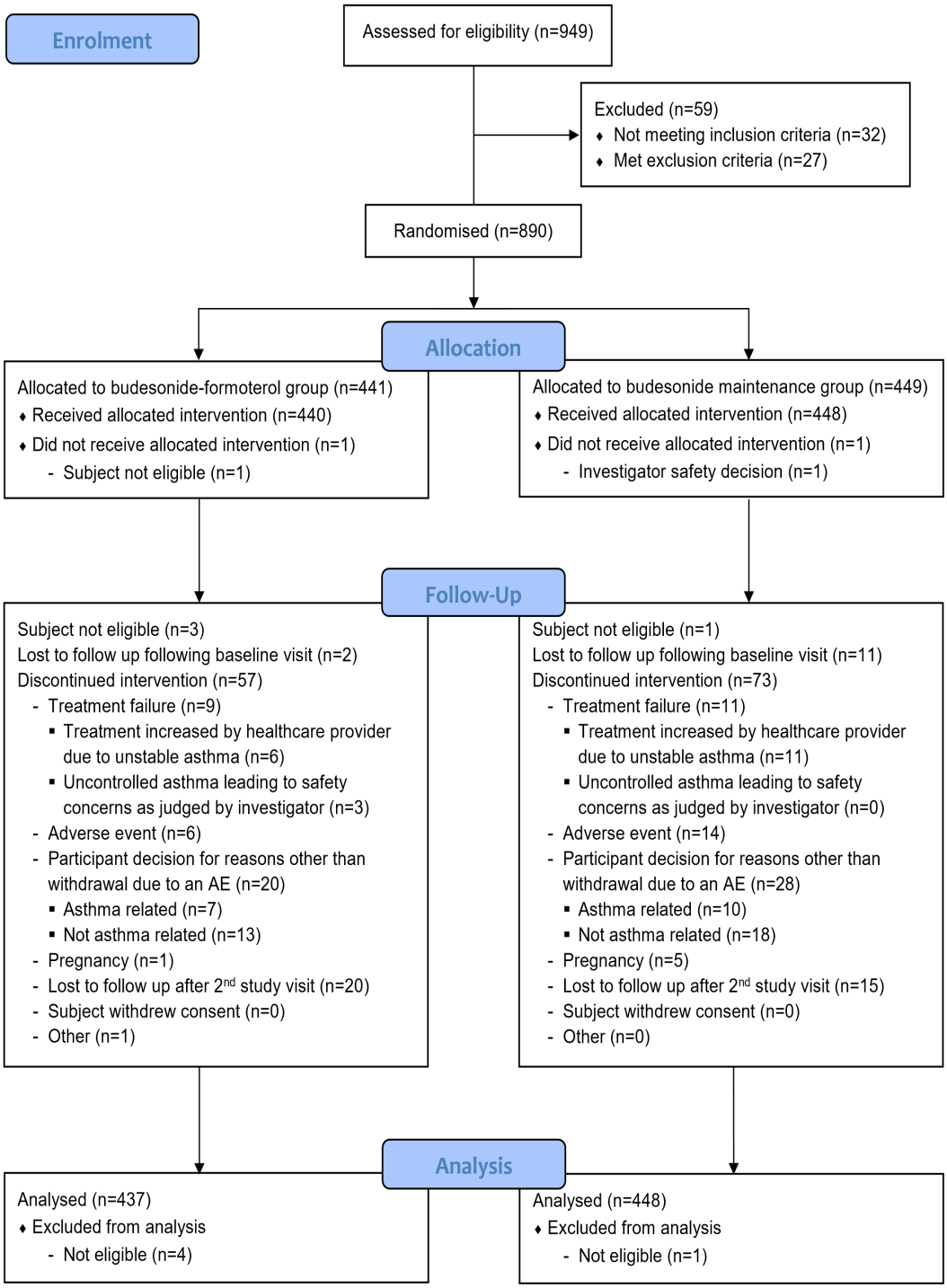

Figure 10: CONSORT diagram of participant flow through the PRACTICAL study

2.4.1. Primary outcome

The primary outcome measure was rate of severe asthma exacerbations per participant per year derived by Poisson regression. The rate of severe exacerbations per participant per year was lower with as-needed budesonide-formoterol than with maintenance budesonide plus terbutaline as needed. The absolute rate per patient per year was 0.119 versus 0.172 with a relative rate of 0.69, (95% confidence interval (95%CI) 0.48 to 1.00), p=0.049 (Figure 11).

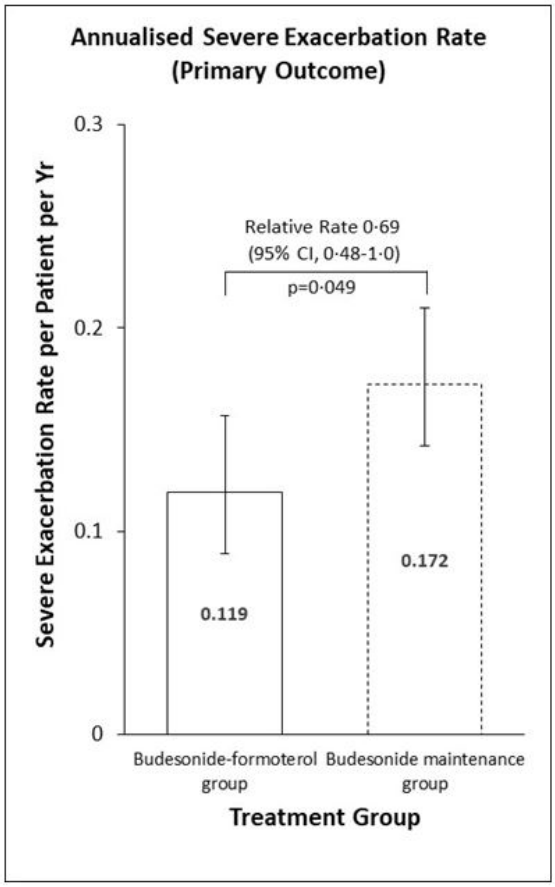

Figure 11: Bar graph of severe exacerbation rate per participant per year

2.4.2. Secondary outcomes

The combined rate of moderate and severe exacerbations per participant per year was lower with as-needed budesonide-formoterol than with maintenance budesonide plus terbutaline as needed. The absolute rate per patient per year was 0.165 versus 0.237 with a relative rate of 0.70, 95%CI 0.51 to 0.95, p=0.024.

Time to first severe asthma exacerbation was longer with as-needed budesonide-formoterol than with maintenance budesonide plus terbutaline as needed with a hazard ratio of 0.60, (95%CI 0.40 to 0.91), p=0.015 (Figure 12).

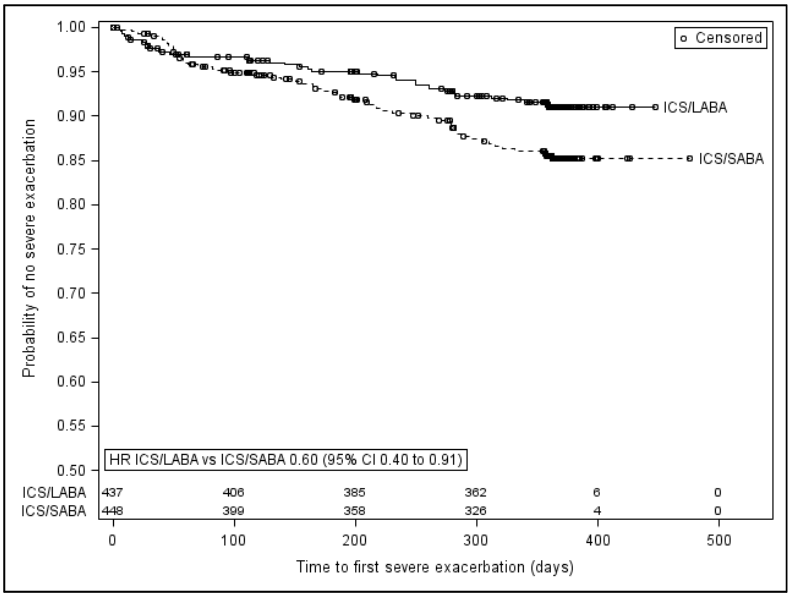

Figure 12: Kaplan Meier curves of time to first severe exacerbation by randomised treatment

Time to first moderate or severe exacerbation was also longer with as-needed budesonide-formoterol than with maintenance budesonide plus terbutaline as needed with a hazard ratio of 0.59, (95%CI 0.41 to 0.84), p=0.004 (Figure 13).

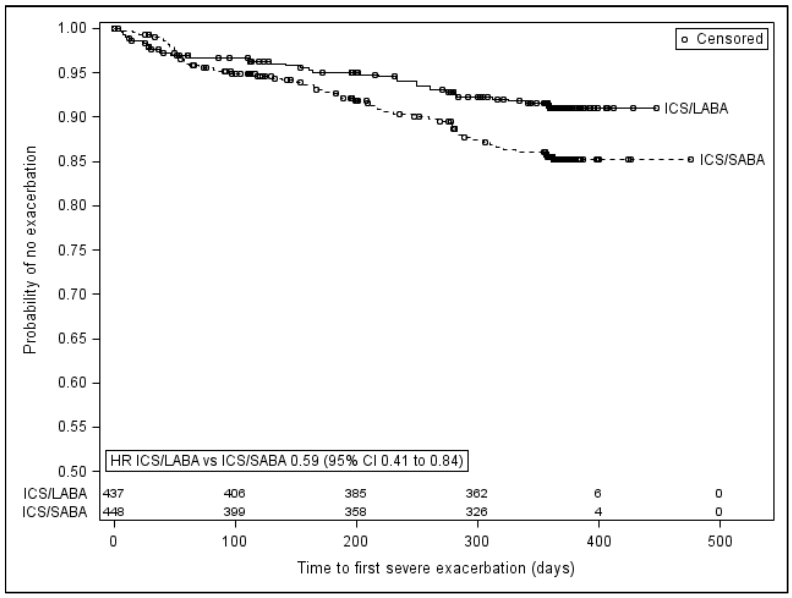

Figure 13: Kaplan Meier curves of time to first moderate or severe exacerbation by randomised treatment

Across all time points ACQ-5 did not differ between as-needed budesonide-formoterol and maintenance budesonide plus terbutaline as needed with a mean difference of 0.06, (95%CI -0.005 to 0.12), p=0.007 averaged over all six times points.

Across all time points on treatment FEV_1 did not differ between as-needed budesonide-formoterol and maintenance budesonide groups with a mean difference of 0.006, (95%CI -0.026 to 0.04), p=0.69 averaged over all three time points.

In the as-needed budesonide-formoterol group median FeNO was 26ppb (parts per billion) (IQR 15 to 51) at randomisation and was 26ppb (IQR 16 to 45) at the final study visit. In the budesonide maintenance group median FeNO was 30ppb (IQR 18 to 62.5) at randomisation and was 25ppb (IQR 16 to 40) at the final study visit. Following randomisation median FeNO across all time points was higher with as-needed budesonide-formoterol than maintenance budesonide (Table 13). Baseline use of ICS affected the response of FeNO to randomised treatment. In participants who were not taking ICS at randomisation median FeNO was 32.5ppb (IQR 15 to 61.5) at baseline and 24ppb (IQR 16 to 41) at final study visit in the as-needed budesonide-formoterol group and was 45ppb (IQR 23 to 91.5) at baseline and 27ppb (IQR 16 to 43) at final study visit in the maintenance budesonide group. In those taking ICS at baseline

median FeNO was 25ppb (IQR 15 to 48) at baseline and 27ppb (IQR 17 to 46) in participants randomised to as-needed budesonide-formoterol versus 27.5ppb at baseline (IQR 16.5 to 54) and 24ppb (15 to 39) at final study visit in those randomised to maintenance budesonide. Because FeNO was widely skewed, it was necessary to log transform the data so assumptions of normality were met to enable comparison of the geometric mean FeNO between the two treatment arms. The ratio of geometric means was 1.13, (95%CI 1.07 to 1.21), p<0.001.

Table 13: Median FeNO across all time points

	Median FeNO (ppb)	
Visit	Budesonide-formoterol as needed	Maintenance budesonide
1	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=405

A sensitivity analysis for effect of various subgroups on the severe exacerbation rate did not identify any evidence of an effect modification from age, sex, ethnicity, smoking status, exacerbation history, ICS use at baseline, adherence to ICS at baseline, baseline SABA use, baseline blood eosinophils, ACQ, FEV_1 % predicted or FeNO. The point estimate still favoured as-needed budesonide-formoterol after accounting for the potential confounding variables (Figure 14).

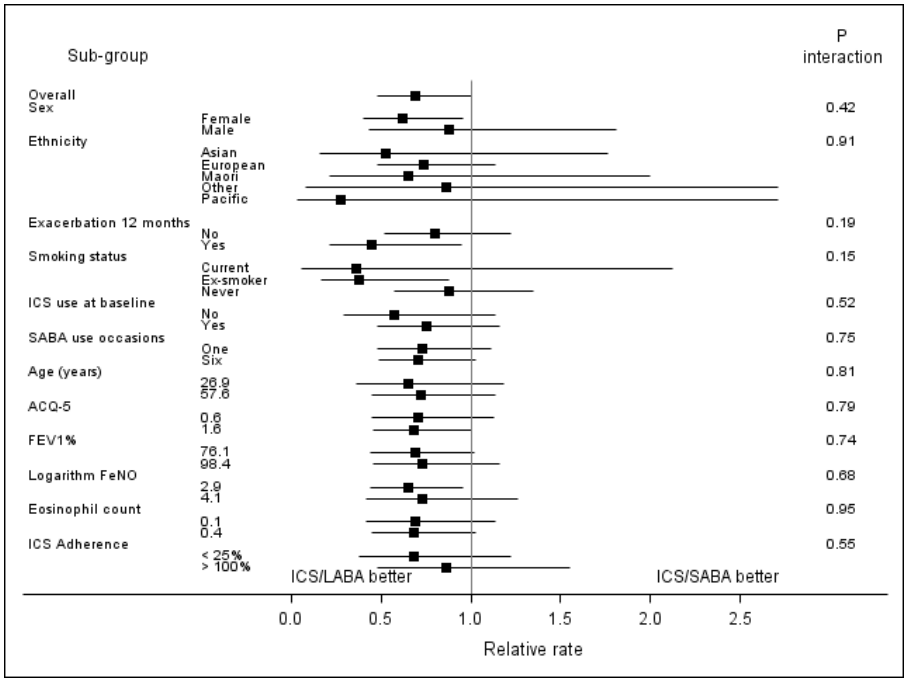

Figure 14: Interaction plot for relative rate of severe exacerbations by potential effect modifying baseline variables

A sensitivity analysis for effect of various subgroups on ACQ-5 score identified that in participants with the highest quartile of baseline blood eosinophils (≥0.4x10^9/L) maintenance budesonide was associated with a greater reduction in ACQ-5. There was no evidence of an effect modification from any of the other variables including age, sex, ethnicity, smoking status, exacerbation history, use of ICS at baseline, adherence to ICS at baseline, baseline SABA use, ACQ, FEV_1 % predicted or FeNO (Figure 15).

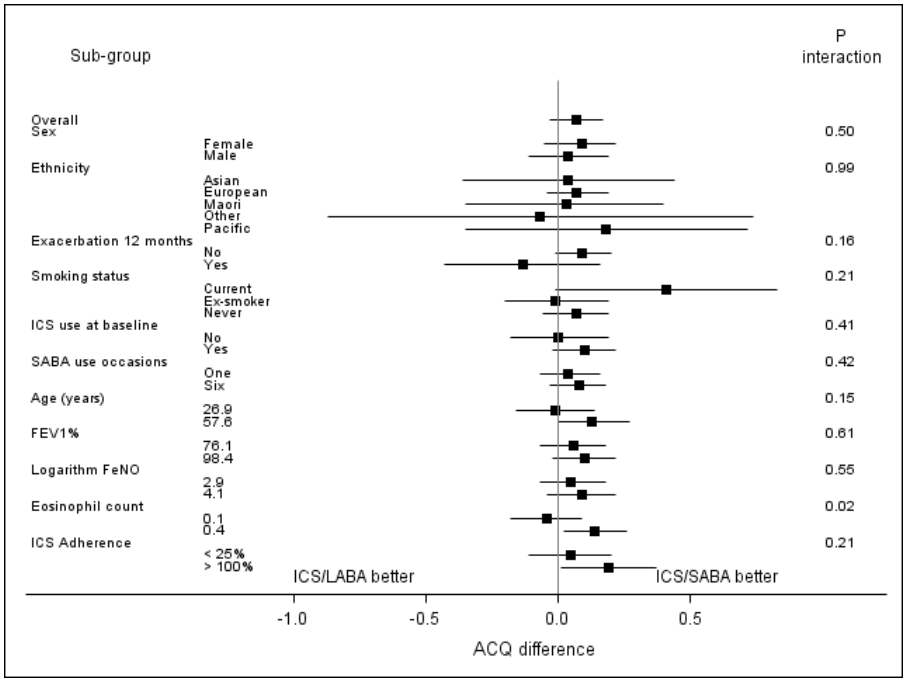

Figure 15: Interaction plot for final study visit ACQ-5 by potential effect modifying baseline variables

Nine participants were withdrawn for treatment failure in the as-needed budesonide-formoterol group and 11 in the maintenance budesonide group. The relative risk of treatment failure between the treatment groups was 0.84, (95%CI 0.35 to 2.00), p=0.69.

Adverse events were similar between the two groups (Table 14), there were two hospitalisations for asthma in the budesonide maintenance groups and there were no deaths during the study.

Table 14: Comparison of adverse events by treatment group

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

2.5. Discussion

The PRACTICAL study found in adults with mild-moderate asthma, as-needed budesonide-formoterol reduced the rate of severe asthma exacerbations by 31% compared to maintenance budesonide plus as-needed terbutaline. The finding from the primary outcome (rate of severe exacerbations) had wide confidence intervals with a p value very close to what would be considered statistically significant. However, the combined rate of moderate and severe exacerbations, and time to first severe exacerbation or first moderate or severe exacerbation all favoured as-needed budesonide-formoterol with less statistical fragility. These secondary outcomes support the finding from the primary outcome and provide evidence that in adults with mild-moderate asthma, as-needed budesonide-formoterol was superior to maintenance budesonide in relation to asthma exacerbations.

The results of the PRACTICAL study complement the results of the Novel START study[178], which also had a real world design. In the Novel START study severe exacerbations (a secondary outcome measure) were 56% lower in those taking as-needed budesonide-formoterol compared to those taking maintenance budesonide. Both studies had wide confidence intervals with p values close to 0.05, however, when considered together they provide greater certainty that as-needed budesonide-formoterol is superior to maintenance budesonide.

The SYGMA 1 and 2[176,177] studies were double blind placebo controlled regulatory trials. They found as-needed budesonide-formoterol was non-inferior to maintenance budesonide with no significant difference in rate of severe exacerbations between the two groups. The differences in severe exacerbation rate between the SYGMA studies and the Novel START and PRACTICAL studies may be related to the differences in study design. The benefits of budesonide-formoterol taken solely as reliever therapy in a real world setting may not be seen in the setting of a rigidly controlled RCT which required regular use of a placebo inhaler. Nonetheless, all four studies complement each other and together there is strong evidence that as-needed budesonide-formoterol is non-inferior to maintenance budesonide for severe asthma

exacerbations, and modest evidence that it is superior. Therefore as-needed budesonide-formoterol is a viable alternative to maintenance budesonide in mild-moderate asthma.

The finding that as-needed budesonide-formoterol was effective with respect to rate of severe asthma exacerbations is supported by the literature on symptom-driven ICS in asthma which preceded the PRACTICAL, Novel START and SYGMA studies. The IMPACT[167], BEST[169], BASALT[173], and AIFASMA[174] studies all investigated the use of symptom-driven ICS and maintenance ICS in mild-moderate asthma finding that symptom-driven ICS was non-inferior to maintenance ICS with respect to rate of severe asthma exacerbations. The data from the PRACTICAL study has extended these studies, finding that symptom-driven ICS-formoterol is superior to maintenance ICS with respect to rate of severe asthma exacerbations in mild-moderate asthma. The results of the PRACTICAL study are in keeping with the literature on use of ICS-formoterol versus SABA reliever therapy in patients with moderate-severe asthma. A recent meta-analysis in patients with moderate-severe asthma found ICS-formoterol as reliever therapy in addition to maintenance ICS-formoterol was associated with a reduction in the risk of severe asthma exacerbations with a relative risk of 0.68 (95%CI 0.58 to 0.80) compared to SABA reliever therapy in addition to maintenance ICS-formoterol[181].

An intrinsic feature of as-needed budesonide-formoterol is patients need to experience symptoms before taking any ICS. Therefore, a concern with this approach is symptom-driven treatment may lead to a higher burden of symptoms than maintenance treatment. However, in the PRACTICAL study there was no difference in asthma symptoms as measured by the ACQ-5 between the two groups and most participants had well controlled asthma (ACQ-5<1)[180]. The SYGMA and Novel START studies[176–178] found ACQ-5 was higher in participants taking as-needed budesonide-formoterol than those taking maintenance budesonide. However, in these three studies the differences in ACQ-5 between the two treatments ranged from 0.11 to 0.15, well below the minimum clinically important difference of 0.50[180]. Together this

indicates that while increased burden of asthma symptoms is a theoretical concern, in most patients it will not be a clinical concern.

It is possible that intermittent use of ICS may be associated with a faster decline in FEV_1 than regular use of ICS. In the PRACTICAL study there was no difference in FEV_1 between the groups at the end of the study. This was also the finding of the Novel START study[178]. In the SYGMA 1 study FEV_1 increased in both the as-needed budesonide-formoterol and the maintenance budesonide arms[176]. In the SYGMA 2 study the difference in FEV_1 between the as-needed budesonide-formoterol and maintenance budesonide groups was not clinically significant[283]. While intermittent use of ICS was not correlated with faster decline in FEV_1 over a year, the effect of intermittent use on FEV_1 over a longer period of time is not known.

Type 2 inflammation in the airways is common in asthma, and is highly responsive to ICS. Theoretically intermittent use of ICS in the budesonide-formoterol arm could lead to worsening Type 2 inflammation. However, in the PRACTICAL study ICS taken in response to symptoms did not lead to uncontrolled Type 2 inflammation as measured by FeNO (a biomarker of Type 2 inflammation). As-needed budesonide-formoterol had anti-inflammatory action, particularly in those who were steroid naïve at baseline in whom median FeNO decreased from 32.5ppb at baseline to 24ppb at the end of the study. Whilst FeNO was higher in the budesonide-formoterol arm than in the maintenance budesonide arm at all time points, the ratio of geometrics means was 1.13, which is equivalent to 5ppb. The ATS guidelines propose that a change of at least 20% or 10ppb indicates a significant difference in FeNO[284], therefore, it is unlikely that the difference in FeNO between the as-needed budesonide-formoterol group and the maintenance budesonide group is of clinical significance. These findings are consistent with the Novel START study. FeNO was not measured in the SYGMA 1 and 2 studies.

The sensitivity analyses of interaction between randomised treatment and various subgroups on the rate of severe exacerbations did not find evidence of effect modification from any of the subgroups included, and the point estimate favoured as-needed budesonide-formoterol. The sensitivity analysis of interaction between

randomised treatment and subgroups on ACQ-5 found that only those participants with blood eosinophils in the highest quartile at baseline had a significant reduction in ACQ-5 with maintenance budesonide. Otherwise all subgroups favoured as-needed budesonide-formoterol. This suggests that treatment effect was consistent across all subgroups of participants and there was not a group of patients who would benefit more from maintenance budesonide with respect to severe exacerbations, and only those with high eosinophils may benefit more from maintenance budesonide with respect to ACQ-5. Therefore, clinical profiling based on patient characteristics is not required and factors such as patient preferences and management priorities should inform decisions on whether to prescribe as-needed budesonide-formoterol or a maintenance ICS regimen.

The majority of adverse events in the PRACTICAL study were minor and the most common adverse event was nasopharyngitis. There were two hospital admissions for asthma in the maintenance budesonide group and no deaths in either group. There was no evidence that use of as-needed budesonide-formoterol was associated with an increase in adverse events or hospitalisation from asthma compared to maintenance budesonide. This combined with the decrease in risk of a severe exacerbation indicates that as-needed budesonide-formoterol in mild-moderate asthma is a safe alternative to maintenance budesonide.

2.5.1. Strengths and weaknesses

Weakness of the PRACTICAL study are the open label design and lack of blinding mean it was susceptible to bias both at the investigator and participant level. However, all of the clinical outcomes used (severe and moderate exacerbation rate, ACQ-5, FEV_1, FeNO) were objective so were less likely to be affected by ascertainment bias than subjective measures[285]. However, the open label nature was the only design which would allow the advantage of as-needed budesonide-formoterol to be properly investigated as blinding and the use of regular placebo inhalers would have meant that the effect on behaviour of taking a single inhaler only as needed would be lost. Use of the same inhaler device for all medications used within the study mean that

differences observed between the treatment groups were not due to differences in inhaler technique and drug delivery between the two arms.

Regular study visits (six within the space of a year) had the potential to influence behaviour, as patients would not usually see a healthcare provider for their asthma as regularly in clinical practice. There is evidence that participation in a clinical trial can have a positive effect on patient outcomes[286]. However, this is likely to have affected both groups equally. Participants who withdrew early were not followed up beyond the point of withdrawal, the two randomised treatment groups may have had different exacerbation rates following withdrawal but this is not possible to determine.

The inclusion criteria for the study were broad and included smokers. Diagnosis of asthma was self-reported and not verified, and participants were not required to demonstrate reversibility. This means that some patients included in the study may not have had a "true" diagnosis of asthma. However, the broad inclusion criteria mean that the study results are generalisable to a wider proportion of the population with a label of asthma. Because the PRACTICAL study explicitly excluded patients with a self-reported diagnosis of COPD or a smoking history of more than 20 pack years the results are not generalisable to patients who have a diagnosis of both asthma and COPD.

The primary outcome, relative rate of severe exacerbations per patient per year had wide confidence intervals with an upper limit of 1.0 and a p value of 0.049 so the finding that as-needed budesonide-formoterol was superior to maintenance budesonide only just achieved statistical significance. However, the secondary outcomes of combined rate of moderate and severe exacerbations and time to first severe exacerbation were in line with the primary outcome and showed that as-needed budesonide-formoterol was the superior treatment and with less statistical fragility. Secondary outcomes were not adjusted for multiplicity of analysis, therefore, there is potential for type 1 error inflation and secondary outcomes should not considered to be definitive.

Strengths of the PRACTICAL study include the rigorous nature in which it was conducted. 10% of all data points were independently monitored and all exacerbations and severe exacerbations of asthma were verified. Therefore, the data is of high quality. Whilst the participants and investigators were un-blinded the study statistician was blinded until analysis of the primary outcome variable was complete, all analyses were pre-specified and a sensitivity analysis of the relative rate of severe asthma exacerbations was robust to all included covariates. This suggests that the result of the primary outcome was not confounded by baseline characteristics such as pre-study ICS use. The real world open label design of the study along with the broad inclusion criteria mean that the results are more likely to be generalisable to routine clinical practice and are less likely to be subject to the gap in efficacy seen between some RCTs and clinical practice[287].

2.5.2. Future work

A meta-analysis of the data from the PRACTICAL, Novel START and SYGMA studies would provide tighter confidence intervals for overall risk of severe exacerbations and provide statistical power to assess less common but serious outcomes measures such as emergency department visits or hospitalisation due to asthma.

The evidence from the SYGMA 1 and 2 studies[176,177] led to ICS-formoterol as needed being recommended at Step 1 and Step 2 of the 2019 GINA update[288]. It would seem intuitive that the effects of as-needed budesonide-formoterol seen in the PRACTICAL, Novel START[178] and SYGMA studies are due to a class effect of ICS, not due to budesonide so are generalisable to other ICS-formoterol formulations. However, clinical trial utilising other formulations of ICS-formoterol are needed to confirm this hypothesis. In addition, the ratio of dose of ICS to formoterol to optimise benefit would need careful consideration if alternative formulations of ICS are used.

The SYGMA studies recruited adolescents aged 12 and up, however, there is no data on the use of as-needed budesonide-formoterol in children. Two studies have reported use of symptom-driven ICS in children[170,172] but in both studies symptom-driven ICS was in a separate inhaler to the reliever medications and a SABA was used

instead of formoterol. Therefore, RCTs in children investigating the use of as-needed budesonide-formoterol are needed to provide evidence on the efficacy and potential side effects such as growth retardation.

There is interest in the use of symptom-driven ICS-SABA as an alternative to budesonide-formoterol, as it would provide an alternative anti-inflammatory reliever option for patients. This approach was investigated as a proof of concept by the BEST study[169] in patients with mild asthma. Symptom-driven ICS-SABA could be used in patients taking different maintenance ICS-LABA combinations such as fluticasone-vilanterol in whom there is no evidence base for addition of a second LABA (such as formoterol), and this may present a safety concern. However, if an ICS-SABA was used, particularly if used as monotherapy it cannot be assumed that replacing formoterol with a SABA would have the same magnitude of clinical benefit, given that formoterol has additional benefits over SABA in preventing asthma exacerbations[158]. Therefore, RCTs investigating the use of ICS-SABA reliever therapy are needed across the range of asthma severities.

Efficacy and safety of ICS-formoterol as needed in the long term has not been studied as the PRACTICAL, Novel START and SYGMA studies were all one year long. A study into use of as-needed budesonide-formoterol over a longer time period such as five years would provide information on rate of lung function decline, and exacerbations over a longer time course. However, it would be expensive and time consuming to run. As ICS-formoterol as needed moves into clinical practice, observational data on outcomes in patients using this regimen may provide information on efficacy and safety in the long term.

Across all asthma severities, budesonide-formoterol as reliever therapy has been shown to be safer and more effective than SABA reliever therapy either alone or in combination with maintenance budesonide-formoterol therapy[176–178,181,279,289]. A newly diagnosed patient or a patient with mild asthma can be prescribed symptom-driven budesonide-formoterol. However, an appropriate algorithm of how and when to step such a patient up to both maintenance and reliever therapy has not been

defined and how such an approach would perform in clinical practice is unknown. A clinical trial assessing titration of budesonide-formoterol across asthma severities would provide clarity, as recently proposed in the European Respiratory Journal[290].

2.6. Conclusion

In conclusion the PRACTICAL study provides modest evidence that as-needed budesonide-formoterol is superior to maintenance budesonide plus as-needed terbutaline at preventing severe asthma exacerbations in adults with mild-moderate asthma, with similar control of asthma symptoms and Type 2 inflammation, rates of treatment failure and adverse events. Therefore, as-needed budesonide-formoterol is an effective and safe alternative to maintenance budesonide plus terbutaline as needed in adults with mild-moderate asthma.

3. The Electronic Monitoring Sub-Study

3.1. Introduction

The PRACTICAL study found symptom-driven budesonide-formoterol was superior to maintenance budesonide plus terbutaline as needed in reducing rate of severe asthma exacerbations. However, how it achieved this effect is unclear. The SYGMA 1 and 2 and Novel START studies[176–178] found as-needed budesonide-formoterol was either non-inferior or superior to maintenance budesonide plus as-needed SABA with respect to severe exacerbation rate. These studies used electronic inhaler monitors to quantify budesonide exposure which allowed them to determine that participants randomised to as-needed budesonide-formoterol used 30% to 48% of the dose budesonide compared to participants randomised to maintenance budesonide plus as needed SABA (see Table 5). This demonstrates that as-needed budesonide-formoterol is effective at reducing severe exacerbation risk at a substantially lower exposure to maintenance budesonide. While summated data on budesonide use was reported, no data on patterns of budesonide or beta$_2$-agonist use has been presented, which would inform on how as-needed budesonide-formoterol achieves its therapeutic benefits.

Therefore, the next step is to determine if the same relationship between budesonide exposure and severe exacerbation risk in the SYGMA and Novel START studies is replicated in the PRACTICAL study, and to explore reasons why this relationship is observed. It may be that patterns of inhaler use, timing of use and titrating dosing of ICS in response to asthma symptoms is important.

Electronic inhaler monitors accurately measure the number of times a patient uses an inhaler, and the time and date the inhaler was used[215] and are more accurate than other methods of measuring adherence[198]. In addition to determining cumulative dose, electronic inhaler monitors can provide information on patterns of inhaler use because each actuation is time and date stamped. Despite electronic inhaler monitors being used in many RCTs and observational studies there is a paucity of data beyond summative data of cumulative use. This represents a missed opportunity to

understand how patients are using their inhalers and how patterns of use relate to outcomes.

Within the PRACTICAL study, a sub group of 110 participants had electronic inhaler monitors attached to their study inhalers. This allowed exposure to budesonide and $beta_2$-agonists, and patterns of inhaler use, in both randomised treatment groups to be investigated. The electronic monitoring sub-study addresses the second aim of this thesis.

The electronic monitoring sub-study was published in The European Respiratory Journal in May 2020[291]. As an author of the published article I retain the right to include it in a thesis or dissertation, provided it is not published commercially. Permission is not required.

3.2. Aim

The primary aim of the electronic monitoring sub-study was to determine usage of ICS in both randomised treatment arms.

Secondary aims were:

i. To investigate patterns of inhaler use across the whole study

ii. To investigate patterns of inhaler use before and after an asthma exacerbation

iii. To investigate the frequency of episodes of $beta_2$-agonist overuse

iv. To determine if any differences in study outcomes existed by inclusion in the electronic monitoring sub-study or not

3.3. Methods

3.3.1. Study design

In a nested sub-study of the PRACTICAL study 110 participants had an electronic inhaler monitor attached to all their study inhalers which recorded the date and time of all actuations. Participants were recruited, and followed up in the same manner as in the wider study and randomised 1:1 to either budesonide-formoterol Turbuhaler (Symbicort) 200/6mcg one inhalation for relief of symptoms as required, or budesonide Turbuhaler (Pulmicort) 200mcg, one inhalation twice a day plus terbutaline (Bricanyl) 250mcg two inhalations as required for relief of symptoms.

3.3.2. Participants

110 participants were recruited from two of the 15 sites in the PRACTICAL study, with a third of participants taking SABA only at baseline. This was to ensure there was sufficient power to detect a difference in outcome according for baseline ICS use. The inclusion and exclusion criteria for the electronic monitoring sub-study were the same as the wider PRACTICAL study.

3.3.3. Study interventions

Electronic inhaler monitors were purchased from Adherium Ltd, Auckland, New Zealand. They record the time and date each time the inhaler is actuated and have previously been validated to have 99.9% accuracy at recording actuations during bench testing[215] and have been successfully used in RCTs[148,160,176–178]. Electronic inhaler monitors were attached to the base of all study inhalers as shown in Figure 16. Prior to dispensing and at each study visit each monitor was checked to ensure there was sufficient power in the monitor's battery and data were being recorded accurately. Any faulty monitors were replaced. Data from the electronic inhaler monitors was downloaded at each study visit. Further details of the procedures used to check the accuracy and data quality from the electronic inhaler monitors are provided in Appendix 8.4. The outcome of all electronic monitors dispensed to participants is located in Appendix 8.5. Participants were told the monitors recorded

the number of times they used their inhaler. The data from the monitors was not viewed during the study except to carry out monitor data quality checks and the participants were made aware of this. All participants in the PRACTICAL study were provided with an asthma plan which stated if they used more than 8 actuations of budesonide-formoterol or 16 actuations of terbutaline they should seek medical advice. The asthma plans are located in Appendix 8.3.

Figure 16: Study inhaler with electronic monitor attached

3.3.4. Definitions

The following definitions were used in the electronic monitoring sub-study:

- A day was defined as the 24 hour period from midnight to midnight.
- A week of no ICS use was defined as seven consecutive days of no ICS use, a fortnight of no ICS use was defined as 14 consecutive days of no ICS use.
- Day 0 was the day when a participant first met the criteria of a moderate or severe exacerbation.

- The period before a moderate or severe exacerbation was the 14 days prior to the day where the participant first met either the moderate or severe exacerbation criteria.
- The period after a moderate or severe exacerbation was the 14 days following the day when the participant first met either the moderate or severe exacerbation criteria.
- The therapeutic ratio between formoterol and terbutaline was defined as one actuation of formoterol 6mcg/actuation being equivalent to two actuations of terbutaline 250mcg/actuation. This definition is based on studies showing similar bronchodilation with repeated use of formoterol at a dose of 6mcg and terbutaline at a dose of 1 x 500mcg [79–81] and from the data sheets for these drugs[82,83].
- High $beta_2$-agonist use was defined as >16 actuations of terbutaline or >8 actuations of budesonide-formoterol per 24 hour period.
- A high $beta_2$-agonist use episode without medical review was defined as overuse on without medical review within two, seven or 14 days of the overuse episode. Overuse within a seven day period following medical review was permitted.[154]

3.3.5. Outcomes

The primary outcome for the electronic monitoring sub-study was mean dose of ICS per day (budesonide mcg/day).

Secondary outcomes are listed in Table 15.

Table 15: Secondary outcomes for electronic monitoring sub-study

Secondary outcomes
ICS outcomes
Proportion of participants with at least one day of no budesonide use
Number of days of no budesonide use
Number of weeks (≥7 consecutive day period) of no budesonide use
Number of fortnights (≥14 consecutive day period) of no budesonide use.
Longest duration of no budesonide use (days)
Maximum number of budesonide actuations in a single day
Number of days when the participant took ≥2/4/6 actuations of budesonide
Beta$_2$-agonist outcomes
Maximum number of beta$_2$-agonist actuations in a single day
Number of days when the participant took ≥2/4 actuations and ≥4/8 actuations of formoterol/terbutaline
Proportion of participants with at least one episode of beta$_2$-agonist overuse
Number of days of beta$_2$-agonist overuse
Number of over beta$_2$-agonist overuse episodes without medical review within 2, 7 and 14 days
Relationship between asthma exacerbations and overuse episodes in relation to randomised treatment
Patterns of inhaler use around asthma exacerbations
Use of budesonide and beta$_2$-agonist before and after an asthma exacerbation
Comparison of number of actuations of budesonide and beta$_2$-agonist before and after a moderate or severe exacerbation
Patterns of inhaler use before and after a moderate or severe exacerbation
Comparison of outcomes by inclusion in the electronic monitoring sub-study or not
Rate of sever exacerbations
End of study ACQ-5
End of study FeNO

3.3.6. Sample size calculation

The primary outcome variable for the electronic monitoring sub-study was mean ICS dose per day. Assuming a dropout rate of 10%, 110 patients were recruited into the sub-study to ensure a sample size of 50 completed patients in each treatment arm, resulting in 90% power, alpha of 5%, to detect a 18% decrease in ICS use (µg/day) with as-needed budesonide-formoterol, compared with 264 mcg/day in the maintenance budesonide arm. This calculation is based on data from a previous study of ICS adherence in stable at-risk patients prescribed regular budesonide/formoterol in which participants took a mean (SD) 66% (27) of their prescribed ICS dose[144].

3.3.7. Statistical analysis

Continuous variables are summarised by mean and SD or median and IQR, and categorical variables by counts and proportions (expressed as percentages).

The primary analysis of electronic monitoring sub-study was comparison of the mean budesonide dose per day by t-test. Comparison of the number of days and weeks and fortnights of no ICS use were analysed by Mann-Whitney test and Hodges-Lehmann estimator of locations difference. Descriptive summaries of longest consecutive number of days of no ICS use, maximum number of actuations of budesonide or $beta_2$-agonist in a single day and number of days when ≥2/4/6 actuations of budesonide or $beta_2$-agonist were taken.

Logistic regression was used to compare the proportions of participants with at least one overuse episode and comparison of rates of overuse was by Poisson regression with an offset for time in study. No analysis between rates of overuse and asthma exacerbations was possible due to the sparsity of the data.

Outcomes in relation to inhaler use around asthma exacerbations were; individual plots of number of inhaler actuations per day for each medication with LOESS plots (locally weighted scatterplot smoothing) showing cumulative use for each medication; quantitative summaries of the number of actuations of each medication in the 14 day and 5 day period before and after an exacerbation; comparison of the number of actuations of each medication before and after an exacerbation using mixed linear model with an interaction term to test if actuation count before and after differed.

Severe exacerbation rate was analysed by Poisson regression with an offset for length of time in study, FeNO was analysed on a logarithmic scale as the data was highly skewed, the differences were analysed as the ratio of geometric means. ACQ-5 was analysed by ANCOVA. An interaction analysis tested if there was a difference in relative rate of severe exacerbations, ACQ-5 and FeNO by randomised treatment inclusion in the electronic monitoring sub-study or not.

No adjustment was made for multiplicity of analyses, therefore, all outcomes except the primary outcome should be considered to be exploratory.

SAS version 9.4 was used for all analyses.

3.4. Results

Baseline demographics for participants in the electronic monitoring sub-study by randomised treatment arm are given in Table 16. Participants randomised to as-needed budesonide-formoterol had a lower self-reported adherence but were otherwise similar with respect to their baseline characteristics. Comparison of baseline demographics between those participants who were enrolled in the electronic monitoring sub-study or not is given in Table 17. Participants enrolled into the electronic monitoring sub-study were on average 7 years older at randomisation and 5 years older at diagnosis but were otherwise similar with respect to their baseline characteristics.

Table 16: Baseline demographics of participants in the electronic monitoring study by randomised treatment

Characteristic	Budesonide-formoterol as needed (n=55)	Maintenance budesonide plus terbutaline as needed (n=55)
Age (years)	48.1 (14)	51.4 (14)
Age at diagnosis (years)	23.1 (20)	23.3 (19.2)
Female sex no.(%)	28 (51)	28 (51)
Ethnicity no.(%)		
Asian	1 (2)	2 (4)
European	45 (82)	46 (84)
Māori	4 (7)	3 (6)
Other	1 (2)	2 (4)
Pacific	4 (7)	2 (4)
Smoking status no.(%)		
Current	1 (2)	2 (4)
Ex-smoker	13 (24)	20 (36)
Never	41 (75)	33 (60)
Pack years (ever smokers)	4.9 (4.8)	6.2 (5.9)
ICS use at randomisation no.(%)*	36 (66)	37 (67)
Self-reported adherence to ICS¥	50.4 (34.8)	60.1 (33.8)
ICS use ever no.(%)	51 (93)	47 (86)
Weekly occasions of SABA use	3.7 (4.9)	3.3 (4.1)
One or more severe exacerbations in the preceding 12 months no.(%)	4 (7)	6 (11)
ACQ-5†	1.1 (0.9)	0.9 (0.7)
FEV_1 % predicted	87.4 (15.3)	88.4 (14.4)
FeNO ppb	23 (14 to 63)	19 (12 to 31)
Blood eosinophil count ($x10^9$ per L)	0.3 (0.2)	0.2 (0.2)

Values are expressed as means (SD) or median (IQR) unless otherwise indicated

* Participants self-reported ICS use in the 12 weeks prior to randomisation

¥ Participant self-reported adherence to ICS in the 4 weeks prior to enrolment (% prescribed dose)

† The Asthma Control Questionnaire–5 (ACQ-5) consists of five questions that assess asthma symptoms in the previous week

Table 17: Comparison of baseline characteristics by inclusion in electronic monitoring sub-study or not

Characteristic	Enrolled in electronic monitoring sub-study (n=110)	Not enrolled in electronic monitoring sub-study (n=775)
Age (years)	49.8 (14)	42.1 (16)
Age at diagnosis (years)	23.2 (19.5)	18.6 (17.6)
Female sex no.(%)	56 (51)	429 (55.4)
Smoking status no.(%)		
Current	3 (3)	60 (8)
Ex-smoker	33 (30)	202 (26)
Never	74 (67)	513 (66)
Pack years (ever smokers)	5.7 (5.4) N=36	4.4 (4.6) N=262
ICS use ever no.(%)	98 (89)	673 (87)
ICS use at randomisation no.(%)*	73 (66)	548 (71)
Self-reported adherence to ICS¥	55.3 (34.4) N=73	56.9 (43.5) N=546
Weekly occasions of SABA use	3.5 (4.5)	4.8 (7.1)
One or more severe exacerbations in the preceding 12 months no.(%)	10 (9)	95 (12)
ACQ-5†	1.0 (0.8)	1.2 (0.8)
FEV_1 % predicted	87.9 (14.8)	87.6 (16.6) N=771
FeNO ppb	21.5 (13 to 47)	30 (17 to 58)
Blood eosinophil count (x10^9 per L)	0.3 (0.2) N=109	0.3 (0.2) N=769

Values are expressed as means (SD) or median (IQR) unless otherwise indicated
* Participants self-reported ICS use in the 12 weeks prior to randomisation
¥ Participant self-reported adherence to ICS in the 4 weeks prior to enrolment (% prescribed dose)
† The Asthma Control Questionnaire–5 (ACQ-5) consists of five questions that assess asthma symptoms in the previous week

3.4.1. ICS use

Mean daily budesonide dose (the primary outcome) was significantly lower with as-needed budesonide-formoterol than with maintenance budesonide (Table 18). The difference was -125.6mcg per day, (95%CI -171.0 to -81.9), p<0.001. Mean adherence to daily budesonide in the budesonide maintenance group was 76%. There were three participants (one randomised to as-needed budesonide-formoterol who withdrew after two weeks and two to maintenance budesonide who completed the study) who took ICS every day they were in the study. The number of days, weeks, fortnights and longest period of no ICS use are also given in Table 18. Those randomised to as-needed budesonide-formoterol had significantly more days of no ICS use than those randomised to maintenance budesonide (median 156 versus 22 days, Hodges Lehmann estimation of location difference 119, 95%CI 90 to 191, p<0.001). Over 70%

of those randomised to as-needed budesonide-formoterol had more than 100 days of no ICS use whereas less than 10% of those randomised to maintenance budesonide had more than 100 days of no ICS use (Figure 17). Those randomised to as-needed budesonide-formoterol had significantly more weeks of no ICS use (median 4 versus 0 weeks per participant, Hodges Lehmann estimation of location difference 3, 95%CI 1 to 8, <p0.001), and more fortnights of no ICS use, however median number of fortnights per participant for both groups was 0 (0 versus 0 fortnights, Hodges Lehmann estimation of location difference 0, 95%CI 0 to 2, p<0.001). Those randomised to as-needed budesonide-formoterol had longer maximum number of consecutive days of no ICS use (median 12 versus 3 days). Participants randomised to maintenance budesonide on average took two actuations of ICS on more days than randomised to as-needed budesonide-formoterol. However, those randomised to as-needed budesonide-formoterol took four or six or more actuations of ICS on more days than those randomised to maintenance budesonide and had a higher maximum number of actuations of budesonide in a single day.

Table 18: Patterns of ICS use

	Budesonide-formoterol as needed (n=55)	Maintenance budesonide plus terbutaline as needed (n=55)	
Number of budesonide-containing actuations per day			
Mean (SD)	0.9 (0.7)	1.5 (0.4)	
Median (IQR)	0.8 (0.4 to 1.3)	1.6 (1.2 to 1.8)	
Min to max	0 to 3.4	0.1 to 2.3	
Daily budesonide dose (mcg)			-126.5 (95%CI -171.0 to -81.9) p<0.001
Mean (SD)	176.0 (143.0)	302.5 (84.8)	
Median (IQR)	164.3 (74.0 to 251.7)	328.3 (245.8 to 364.0)	
Min to max	6.7 to 682.5	26.8 to 458.1	
Mean adherence	n/a	76%	
Number of days no ICS use			119 (95%CI 90 to 191) p<0.001
Mean	182 (109.4)	45.9 (64.6)	
Median	156 (95 to 284)	22 (6 to 70)	
Min to max	0 to 352	0 to 327	
Number of weeks of no ICS use			3 (95%CI 1 to 8) p<0.001
Mean	12.6 (15.4)	1.8 (6.6)	
Median	4 (0 to 24)	0 (0 to 1)	
Min to max	0 to 48	0 to 38	
Number of fortnights of no ICS use			0 (95%CI 0 to 2) p<0.001
Mean	4.6 (6.8)	0.7 (2.8)	
Median	0 (0 to 7)	0 (0 to 0)	
Min to max	0 to 23	0 to 17	
Longest period of no ICS use (days)			
Mean	40.3 (59.9)	8.7 (19.4)	
Median	12 (5 to 48)	3 (1 to 8)	
Min to max	0 to 260	0 to 129	
Maximum number of actuations in a single day			
Mean	6.0 (2.9)	4.3 (2.0)	
Median	5 (4 to 8)	4 (3 to 5)	
Min to max	1 to 13	2 to 14	
Number of days ≥2 actuations			
Mean	75.9 (72.8)	194.0 (89.7)	
Median	48 (14 to 114)	204 (122.5 to 273)	
Min to max	0 to 329	14 to 333	
Number of days ≥4 actuations			
Mean	12.3 (26.0)	3.1 (7.7)	
Median	4 (1 to 10)	1 (0 to 3)	
Min to max	0 to 153	0 to 52	
Number of days ≥6 actuations			
Mean	3.2 (8.2)	0.4 (1.8)	
Median	0 (0 to 2)	0 (0 to 0)	
Min to max	0 to 39	0 to 12	

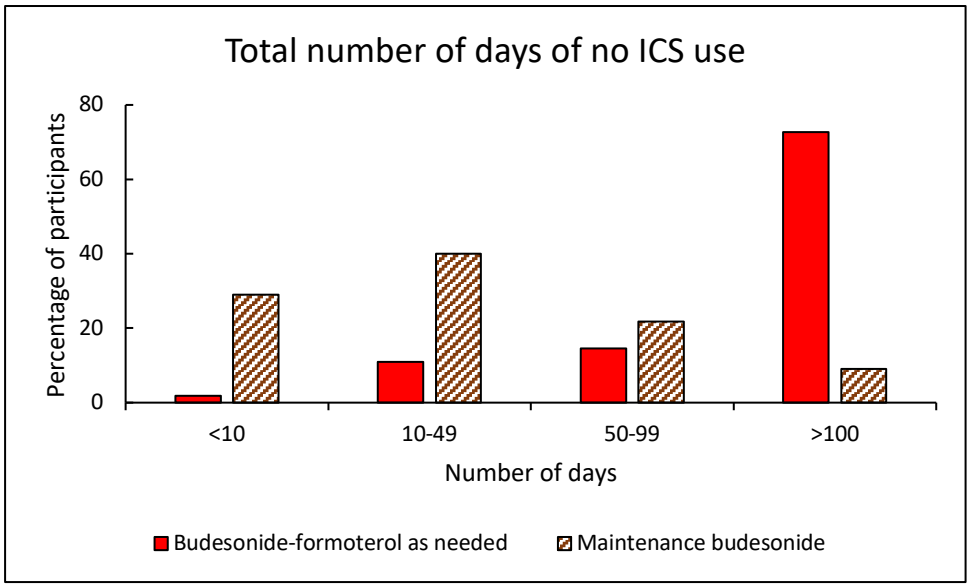

Figure 17: Bar chart of total number of days of no ICS use across the whole study in each randomised treatment group

Budesonide usage in the 16 participants who had 19 severe exacerbations is given in Table 19. The six participants randomised to as-needed budesonide-formoterol who had a severe exacerbation had median of 164 days of no budesonide use and 72 days was the median longest period of no ICS. By comparison the 10 participants randomised to maintenance budesonide who had a severe exacerbation had median of 24 days of no budesonide use and 3.5 days was the median longest period of no budesonide use.

Table 19: Patterns of ICS use in participants who had a severe exacerbation

	Budesonide-formoterol as needed N=6	Maintenance budesonide N=10
Number of budesonide-containing actuations per day		
Mean	1.0 (0.6)	1.6 (0.4)
Median	1.1 (0.6 to 1.5)	1.6 (1.3 to 1.8)
Min to max	0.08 to 1.62	0.89 to 2
Mean Adherence - % of prescribed dose	n/a	77 (17)
Number of days no ICS use		
Mean	176.5 (139.5)	39.6 (35.8)
Median	164 (51.0 to 281.5)	24 (15.5 to 69.25)
Min to max	47 to 350	2 to 103
Number of weeks of no ICS use		
Mean	19.0 (20.1)	0.2(0.4)
Median	16 (1.25 to 33)	0 (0 to 0)
Min to max	0 to 47	0 to 1
Number of fortnights of no ICS use		
Mean	8.3 (9.0)	0 (0)
Median	6.5 (0.5 to 14.75)	0 (0 to 0)
Min to max	0 to 21	0 to 0
Longest period of no ICS use (days)		
Mean	68.8 (65.0)	4.3 (3.8)
Median	72 (9 to 119.25)	3.5 (1.25 to 5)
Min to max	2 to 144	1 to 13

3.4.2. Beta$_2$-agonist use and overuse

For participants randomised to as-needed budesonide-formoterol use of beta$_2$-agonist was the same as use of ICS. Overall those randomised to as-needed budesonide-formoterol took a median of 0.8 actuations of beta$_2$-agonist per day and those randomised to maintenance budesonide took median of 0.3 actuations of beta$_2$-agonist per day (Table 20). The maximum number of actuations of beta$_2$-agonist taken on a single day was median 5 actuations for as-needed budesonide-formoterol and median 6 actuations maintenance budesonide respectively. Use of ≥2 actuations of formoterol or ≥4 actuations of terbutaline occurred on median of 48 vs 3 days, and use of ≥4 actuations of formoterol or ≥8 actuations of terbutaline occurred on median of 4 vs 0 days.

Table 20: Patterns of beta$_2$-agonist use

	Budesonide-formoterol as needed N=55	**Maintenance budesonide N=55**
Beta$_2$-agonist	Formoterol 6mcg	Terbutaline 250mcg
Daily beta$_2$-agonist actuations		
Mean	0.9 (0.7)	0.5 (0.6)
Median	0.8 (0.4 to 1.3)	0.3 (0.1 to 0.6)
Min to max	0 to 3.4	0 to 2.7
Maximum actuations in a single day		
Mean	6.0 (2.9)	8.0 (10.9)
Median	5 (4 to 8)	6 (3 to 9.5)
Min to max	1 to 13	0 to 80
Number days ≥2 actuations of formoterol or ≥4 actuations of terbutaline		
Mean	75.9 (72.8)	12.6 (23.5)
Median	48 (14 to 114)	3 (0 to 14.5)
Min to max	0 to 329	0 to 139
Number days ≥4 actuations of formoterol or ≥8 actuations of terbutaline		
Mean	12.3 (26.0)	1.7 (3.9)
Median	4 (1 to 10)	0 (0 to 2)
Min to max	0 to 153	0 to 21

There were few episodes of beta$_2$-agonist overuse. Of the 110 participants in the electronic monitoring sub-study 15 participants met the criteria for beta$_2$-agonist overuse at least once. Eleven of 55 (20%) participants randomised to as-needed budesonide-formoterol and had 33 days of overuse across the whole study and 4 of 55 (7%) participants randomised to maintenance budesonide had 10 days of overuse across the whole study. The rate of overuse days per year for budesonide-formoterol and maintenance budesonide groups was 0.62 and 0.19 respectively (relative rate 3.3, 95%CI 1.6 to 6.6, p=0.001). Three participants randomised to as-needed budesonide-formoterol had at least one episode of beta$_2$-agonist overuse in the 14 days before an exacerbation. No patients randomised to maintenance budesonide had a beta$_2$-agonist overuse episode in the 14 days before an exacerbation. There were too few days of beta$_2$-agonist overuse to allow any analysis looking at overuse episodes in relation to asthma exacerbations. After an overuse episode no participants sought medical review within 48 hours as was specified on their asthma plan. One participant randomised to as-needed budesonide-formoterol sought medical review within 7 days and another participant within 14 days.

3.4.3. Patterns of inhaler use before and after asthma exacerbations

Nine participants randomised to as-needed budesonide-formoterol had 12 moderate or severe exacerbations, and 13 participants randomised to maintenance budesonide had 15 moderate or severe exacerbations. Table 21 describes the total number of actuations and the mean number of actuations per day for each inhaler in the 14 and five days before and after an exacerbation. The number of ICS actuations per day in the five and 14 day periods before a moderate or severe exacerbation in those randomised to budesonide-formoterol and to maintenance budesonide were a median 1.7 vs. 2.0 and 1.5 vs 1.7 actuations respectively.

The number of beta$_2$-agonist containing actuations per day in the five and 14 days before a moderate or severe exacerbation in those randomised to budesonide-formoterol and maintenance budesonide were a median 1.7 vs. 2.8 and 1.5 vs. 1.8 actuations respectively.

Total number of actuations of ICS were significantly higher in the 14 days before an exacerbation than the 14 days after for those randomised to as-needed budesonide-formoterol (12.4, 95%CI 2.6 to 22.3, p=0.015). There was no evidence that total number of actuations differed in participants randomised to maintenance budesonide for either the budesonide inhaler (0.5, 95%CI -8.4 to 9.3, p=0.92) or the terbutaline inhaler (4.2, 95%CI -7.0 to 15.4, p=0.45).

Table 21: Inhaler actuations before and after a moderate or severe exacerbation

	Budesonide formoterol as needed N=12	Maintenance budesonide plus terbutaline as needed N=15
Budesonide actuations		
Average actuations per day in the 14 days before an exacerbation		
Mean (SD)	2.1 (1.7)	1.7 (0.3)
Median (IQR)	1.5 (0.9 to 2.4)	1.7 (1.5 to 2.0)
Min to max	0.4 to 6.0	1.1 to 2.2
Average actuations per day in the 5 days before to an exacerbation		
Mean (SD)	2.4 (1.6)	2.0 (0.4)
Median (IQR)	1.7 (1.2 to 3.7)	2.0 (1.8 to 2.2)
Min to max	0.8 to 5.2	1.2 to 2.4
Average actuations per day in the 14 days after an exacerbation		
Mean (SD)	1.2 (0.8)	1.2 (0.9)
Median (IQR)	1.0 (0.9 to 2.4)	1.9 (1.4 to 1.9)
Min to max	0 to 3.4	0.4 to 4.1
Average actuations per day in the 5 days after an exacerbation		
Mean (SD)	1.5 (0.7)	1.9 (1.2)
Median (IQR)	1.5 (1.1 to 2.0)	1.8 (1.1 to 1.9)
Min to max	0.8 to 2.4	0.4 to 5.4
Comparison of total number of actuations in 14 days pre and post an exacerbation	12.4 (95%CI 2.6 to 22.3) p=0.015	0.5 (95%CI -8.4 to 9.3) p=0.92
Comparison of total number of actuations in 5 days pre and post an exacerbation	4.6 (95%CI 1 to 8.2) p=0.015	0.3 (95%CI -2.9 to 3.6) p=0.83
Beta$_2$-agonist actuations		
Average actuations per day in 14 days before an exacerbation		
Mean (SD)	2.1 (1.7)	1.9 (1.6)
Median (IQR)	1.5 (0.9 to 2.4)	1.8 (0.7 to 2.9)
Min to max	0.4 to 6.0	0 to 5.9
Average actuations per day in the 5 days before to an exacerbation		
Mean (SD)	2.4 (1.6)	2.8 (1.8)
Median (IQR)	1.7 (1.2 to 3.7)	2.8 (1.6 to 3.8)
Min to max	0.8 to 5.2	0 to 6.2
Average actuations per day in the 14 days after an exacerbation		
Mean (SD)	1.2 (0.8)	1.6 (1.4)
Median (IQR)	1.0 (0.9 to 2.4)	1.1 (0.4 to 2.8)
Min to max	0 to 3.4	0 to 4.1
Average actuations per day in the 5 days after an exacerbation		
Mean (SD)	1.5 (0.7)	2.2 (2.0)
Median (IQR)	1.5 (1.1 to 2.0)	2.0 (0.5 to 3.3)
Min to max	0.8 to .42	0 to 6.0
Comparison of total number of actuations in 14 days pre and post an exacerbation	12.4 (95%CI 2.6 to 22.3) p=0.015	4.2 (95%CI -7.0 to 15.4) p=0.45
Comparison of total number of actuations in 5 days pre and post an exacerbation	4.6 (95%CI 1 to 8.2) p=0.015	2.9 (95%CI -1.7 to 7.5) p=0.20

The summated actuation counts for each inhaler before and after an exacerbation are shown in the LOESS plots in Figure 18 (budesonide-formoterol), Figure 19 (budesonide) and Figure 20 (terbutaline). Overall there was a pattern of participants increasing their use of budesonide-formoterol or terbutaline before an exacerbation and decreasing it after, however these changes were modest. Use of maintenance budesonide before and after an exacerbation remained constant.

Individualised graphs of the number of actuations of budesonide-formoterol used in the 14 days before and after the exacerbation are shown in Figure 21. One participant used 36 actuations on day -14 so their data is presented separately in Figure 22. For those randomised to maintenance budesonide this information is shown in Figure 23 for the budesonide inhaler and Figure 24 for the terbutaline inhaler. These graphs show there was considerable variation in patterns of inhaler use before and after an exacerbation with patterns of high and low ICS and beta$_2$-agonist use in both randomised treatment groups.

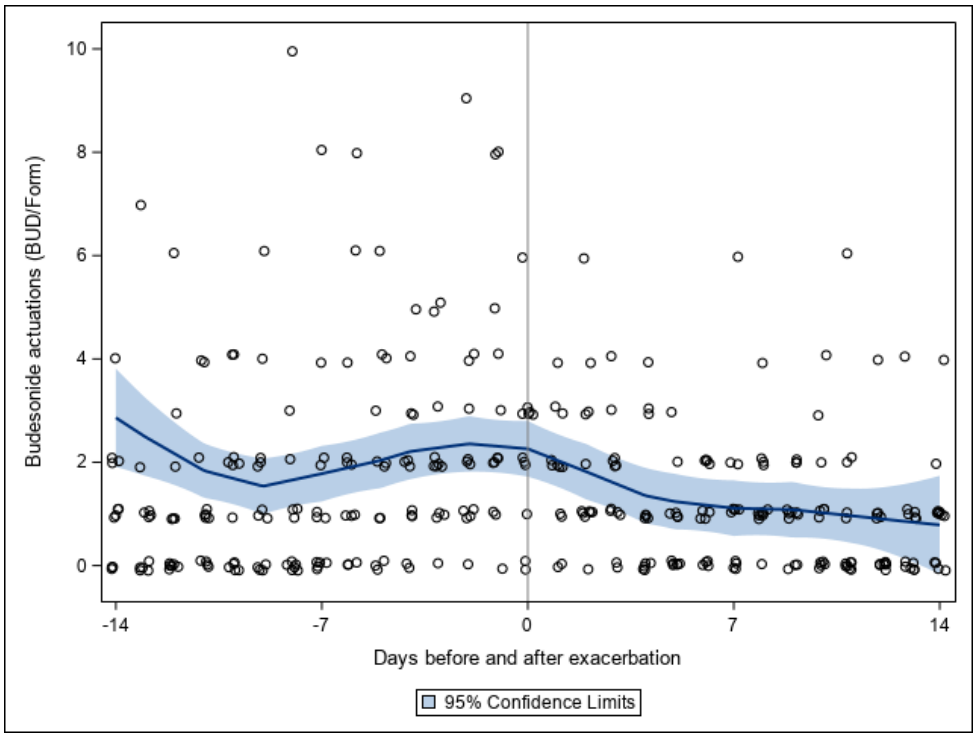

Figure 18: LOESS plot estimating the number of budesonide-formoterol actuations in the 14 days before and after onset of a moderate or severe exacerbation across the participants

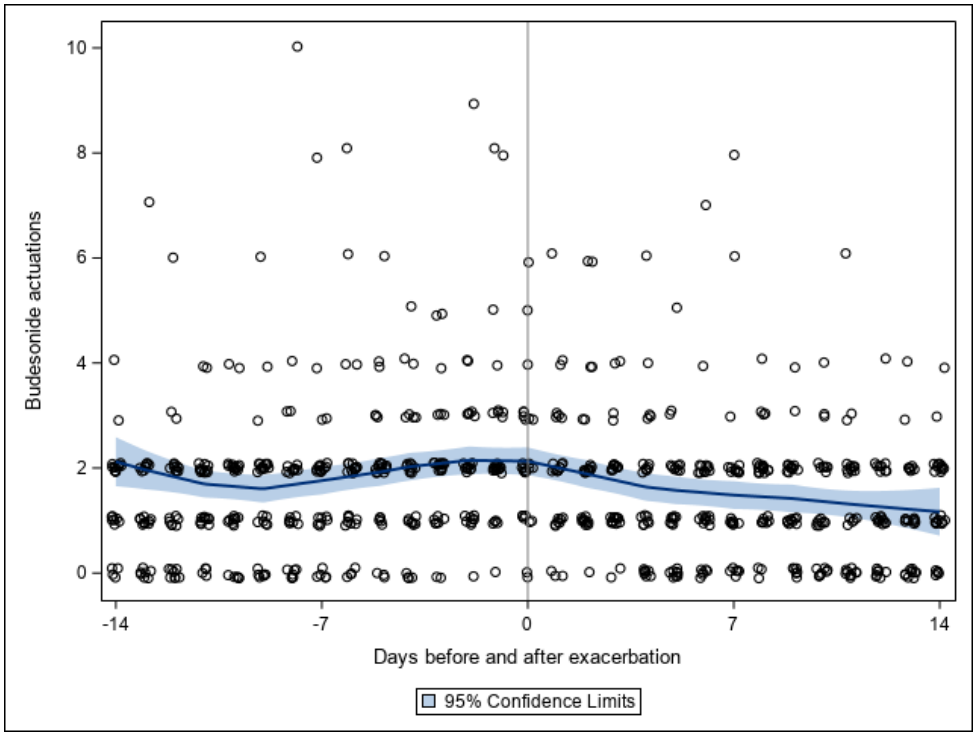

Figure 19: LOESS plot estimating the number of budesonide actuations in the 14 days before and after onset of a moderate or severe exacerbation across the participants

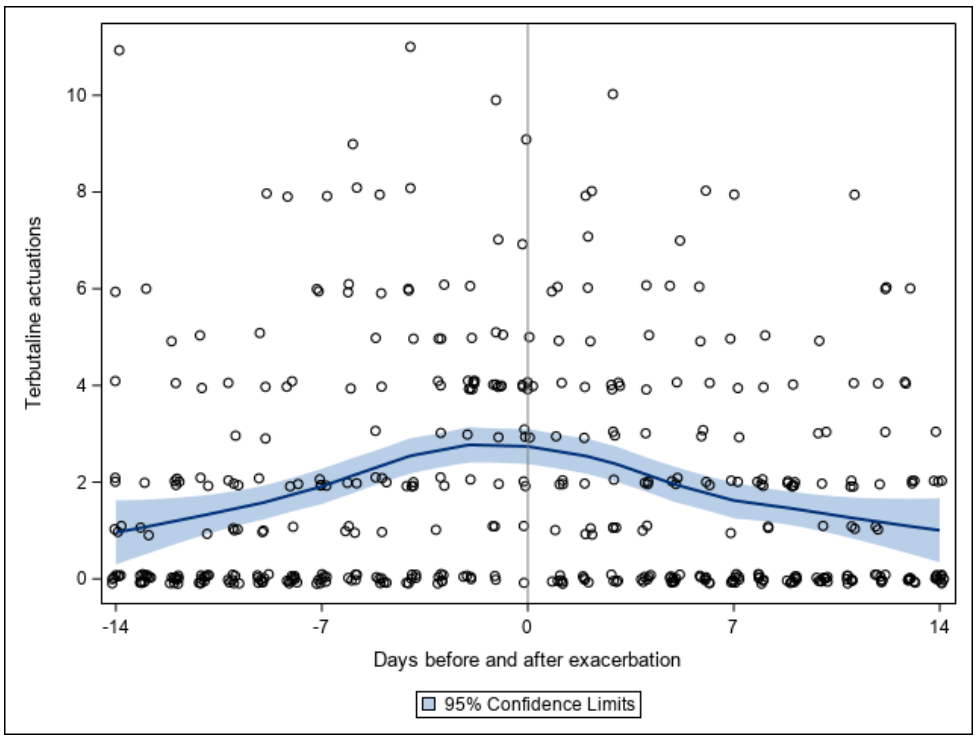

Figure 20: LOESS plot estimating the number of terbutaline actuations in the 14 days before and after onset of a moderate or severe exacerbation across the participants

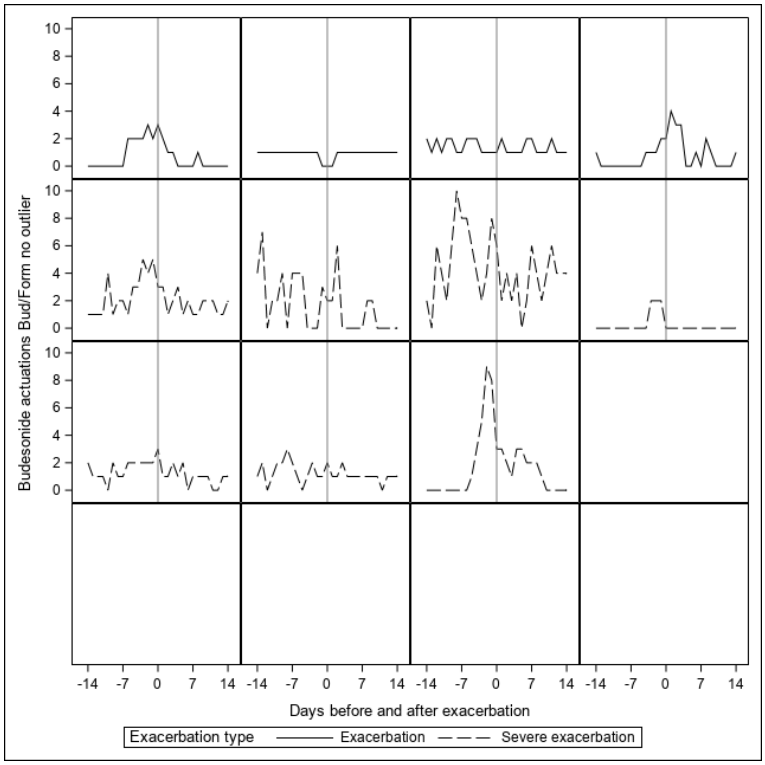

Figure 21: Individual participant use of budesonide-formoterol in the 14 days before and after onset of a moderate or severe exacerbation

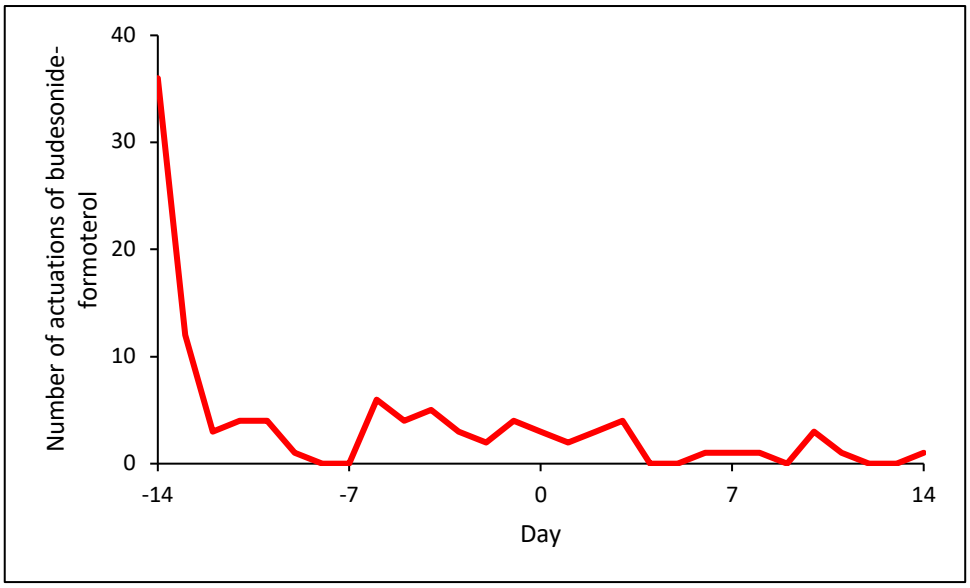

Figure 22: Budesonide-formoterol use in the 14 days before and after onset of an exacerbation in the participant who used of 36 actuations of budesonide-formoterol on day -14

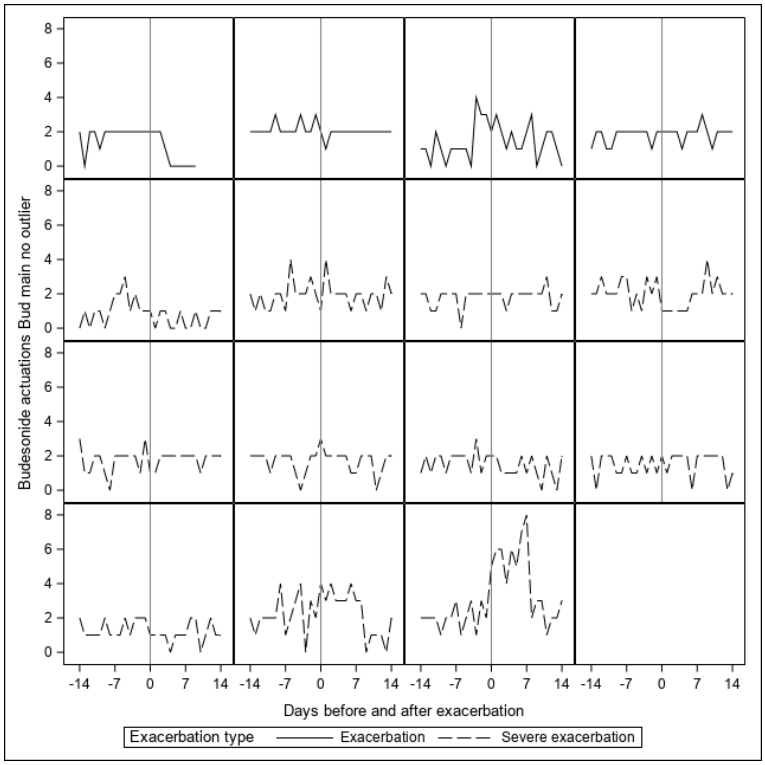

Figure 23: Individual participant use of budesonide in the 14 days before and after onset of a moderate or severe exacerbation

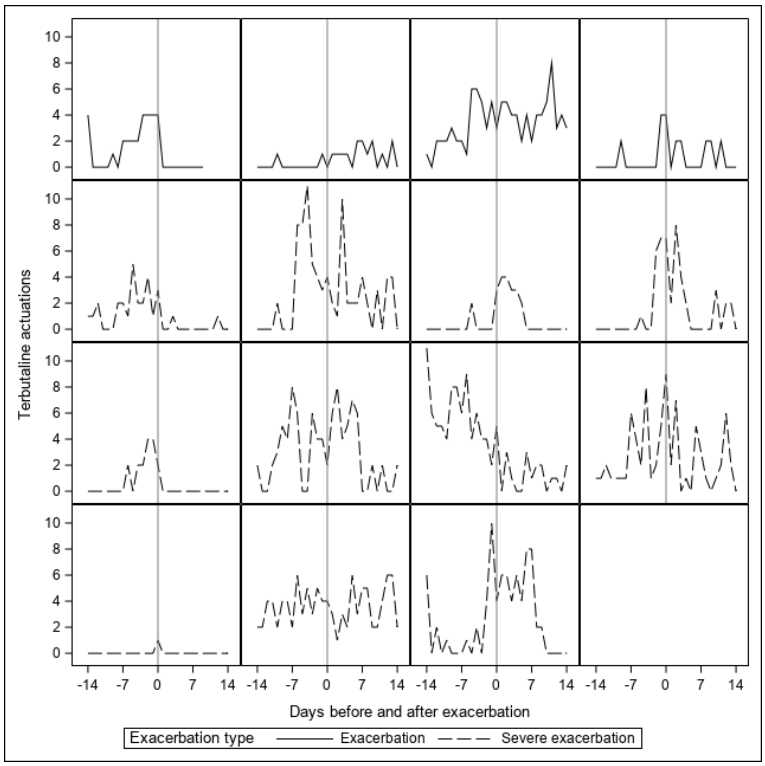

Figure 24: Individual participant use of terbutaline in the 14 days before and after onset of a moderate or severe exacerbation

3.4.4. Comparison of outcomes by inclusion in the electronic monitoring sub-study or not

The relative rate of severe exacerbations, final study visit FeNO and ACQ-5 by randomised treatment and inclusion in the electronic monitoring sub-study or not is given in Table 22. In the electronic monitoring sub-group the rate of severe exacerbations was lower with budesonide-formoterol with a relative rate of 0.72 (95%CI 0.29 to 1.79). Final study visit FeNO was higher in the budesonide-formoterol arm with a ratio geometric means of 1.15 (95%CI 0.94 to 1.39), and ACQ-5 was higher with a difference of 0.14 (95%CI -0.14 to 0.41). These results mirrored the findings from the main PRACTICAL study. There was no evidence of an interaction between inclusion in the electronic monitoring sub-study and randomised treatment for rate of severe exacerbations (p=0.92), FeNO (p=0.89) or ACQ-5 (p=0.50).

Table 22: Study outcomes by enrolment in electronic monitoring sub-study or not

	Budesonide-formoterol as needed		**Maintenance budesonide**		**Interaction between inclusion in electronic monitoring sub-study and outcome**
Study outcome	**Electronic monitoring sub-group N=55**	**Not in electronic monitoring sub-group N=382**	**Electronic monitoring sub-group N=55**	**Not in electronic monitoring sub-group N=393**	
Number of severe exacerbations	8	40	11	57	
Rate of severe exacerbations per participant per year	0.15	0.11	0.21	0.17	p=0.92
FeNO (ppb)	23 (15 to 48)	26 (16 to 45) N=346	18 (13 to 32)	27 (16 to 41) N=351	p=0.89
ACQ-5	0.87 (0.69)	0.86 (0.76) N=348	0.64 (0.72)	0.82 (0.88) N=351	p=0.50

3.5. Discussion

The electronic monitoring sub-study found patients randomised to as-needed budesonide-formoterol used 58% of the dose of budesonide compared to those randomised to maintenance budesonide plus as-needed terbutaline. The PRACTICAL

study found those randomised to as-needed budesonide-formoterol had a lower severe exacerbation rate, with no difference in symptom control. These results complement the findings from the SYGMA 1 and 2 and Novel START studies[176–178] and provides additional evidence that as-needed budesonide-formoterol is more effective at preventing severe exacerbations at a significantly lower exposure to ICS in patients with mild asthma and extends the findings to patients with moderate asthma.

The mechanisms for how as-needed budesonide formoterol achieves its effects are suggested by the noticeably different patterns of both ICS and beta$_2$-agonist use between the as-needed budesonide-formoterol and maintenance budesonide groups. Those using as-needed budesonide-formoterol had significantly more days of no ICS use and longer periods of no use overall. However, they up-titrated their use of ICS to higher levels both overall and in the setting of asthma exacerbations. By design formoterol use was the same as ICS use in those randomised to budesonide-formoterol. Participants randomised to as-needed budesonide-formoterol had higher use of beta$_2$-agonist both overall and during exacerbations, particularly if the therapeutic ratio of one actuation of formoterol 6mcg being equivalent to two actuations of terbutaline 250mcg is considered[79–81]. These findings suggest that in patients with mild-moderate asthma intermittent use of budesonide-formoterol, titrated to symptoms is more effective than daily use of budesonide or cumulative dose in reducing exacerbation risk. The greater doses of beta$_2$-agonist taken during worsening asthma and the use of formoterol rather than a SABA may also contribute.

In the electronic monitoring sub-study, those randomised to maintenance budesonide were highly adherent, taking on average 76% of their prescribed dose with a median of 22 days of no ICS use through the 12 month study period. Whereas those randomised to as-needed budesonide-formoterol had extended periods of no ICS use, with a median of 156 days of no ICS use, equating to over 40% of the days in the study. Despite high adherence to ICS in the maintenance budesonide group within the electronic monitoring sub-study, they had a higher rate of severe exacerbations than the as-needed budesonide-formoterol group.

The participants randomised to as-needed budesonide-formoterol who experienced a severe exacerbation, took a similar number of ICS actuations per day to those who did not. However, they had more weeks, fortnights and greater longest period of no ICS use than the group overall. These participants may represent a sub-group of people for whom as-needed budesonide-formoterol is not appropriate or who did not up-titrate their use effectively in response to symptoms. By contrast the participants randomised to maintenance budesonide who had a severe exacerbation were all highly adherent with no full weeks of no ICS use, suggesting that poor adherence was not the cause of their exacerbations. They may be a sub-group of participants in whom fixed dose maintenance budesonide was not sufficient.

There was evidence that participants in both treatment groups up-titrated use of ICS from baseline during an asthma exacerbation. This was more marked in participants randomised to as-needed budesonide-formoterol who increased their use from a median of 0.8 actuations per day across the whole study to median of 1.7 actuations per day in the five days before an exacerbation, then quickly decreased it after. Patients randomised to maintenance budesonide increased their ICS before an exacerbation to a lesser extent, from median of 1.6 to 2.0 actuations, in the five days before an exacerbation. Individual graphs of ICS use show there was highly variable patterns of ICS use in both treatment groups. Again, this was most evident in participants randomised to as-needed budesonide-formoterol, however participants randomised to maintenance budesonide also up-titrated their ICS use above their prescribed two actuations a day on some days. The LOESS plots of cumulative data convey that use of budesonide-formoterol smoothly increased before then decreased after an exacerbation and use of maintenance budesonide was relatively constant. They do not reveal the considerable day to day variation in use of budesonide-formoterol or that participants randomised to maintenance budesonide were also titrating their use of ICS around an exacerbation, which is apparent from the individual graphs.

Comparing formoterol and terbutaline, two different $beta_2$-agonists presents difficulties as they have different properties in terms of duration of action and there is

evidence that use of formoterol as reliever therapy may reduce severe exacerbations compared to use of a SABA such as terbutaline[84]. In addition, as discussed in this chapter and the Introduction, the therapeutic ratio and directions for use to relieve asthma symptoms for formoterol and terbutaline was one actuation of formoterol 6mcg for two actuations of terbutaline 250mcg.

Across the whole study, overall use of beta$_2$-agonist was low in both groups. When the therapeutic ratio of the two beta$_2$-agonist is considered, participants in the as-needed budesonide-formoterol group had higher beta$_2$-agonist use than those in the maintenance budesonide group; using median of 0.8 versus 0.3 actuations of beta$_2$-agonist a day, which equates to almost five times the amount of the maintenance group. This pattern was mirrored in the number days of beta$_2$-agonist overuse and the number of days participants used ≥2 or 4 actuations of formoterol or ≥4 or 8 actuations of terbutaline.

Participants randomised to as-needed budesonide-formoterol used about twice as much beta$_2$-agonist before an exacerbation than those randomised to maintenance budesonide plus terbutaline as needed. Similar to use of ICS there were highly variable patterns of individual use of beta$_2$-agonists before and after an exacerbation for both terbutaline and budesonide-formoterol, however the LOESS plots suggested a smooth increase in use before an exacerbation followed by a decrease after. This suggests that the model of increasing beta$_2$-agonist use before an exacerbation followed by decreasing use after in the literature[155] may be misleading, as it neglects much of the nuance.

The results of the electronic monitoring sub-study suggest that increasing use of budesonide-formoterol as reliever therapy may have a different outcome to increasing use of terbutaline reliever therapy. Increased use of beta$_2$-agonist was seen in the as-needed budesonide-formoterol group who had a lower rate of severe exacerbations. Discussed in the Introduction, increasing use of SABA is associated with adverse outcomes in asthma including exacerbations, hospitalisation and death from asthma[133,153]. However, increasing use of ICS-formoterol as reliever therapy is likely to

be protective as it leads to increased delivery of ICS via the vehicle of a bronchodilator and the use of formoterol may be providing additional protection against exacerbations than a SABA would[84]. Therefore, the association of increased reliever use and risk of asthma exacerbation that is seen with SABA reliever therapy may not apply to ICS-formoterol reliever therapy.

Consistent with the main study, in the electronic monitoring study randomisation to maintenance budesonide only provided marginal benefits in Th2 inflammation (as measured by FeNO) over use of as-needed budesonide-formoterol. Asthma symptom control (as measured by ACQ-5) was no different between the two groups and rate of severe exacerbations was lower with budesonide-formoterol. This suggests good asthma symptom control and a reduction in severe exacerbations can be achieved with intermittent use of ICS in response to symptoms in patients with mild-moderate asthma.

3.5.1. Strengths and weaknesses

The electronic monitoring sub-study included 110 participants who had electronic inhaler monitors attached to their study inhalers. Therefore, this is a relatively small data set so there is less power to draw definitive conclusions, particularly on secondary outcome measures. No significant difference in clinical outcomes between the electronic monitoring sub-study and the wider PRACTICAL study suggests that the results from this sub-group are likely to be generalisable to the wider PRACTICAL population. Within the electronic monitoring sub-study, seven participants withdrew early (three in the budesonide-formoterol group and 4 in the maintenance budesonide group) which was less that the 10% allowed for in the power calculations. Therefore, the study was adequately powered for the primary outcome – difference in mean ICS dose between the two groups.

Adherence to maintenance budesonide was higher than expected. Use of electronic inhaler monitors may have affected patients' behaviour, so the patterns of use, particularly for maintenance budesonide might not reflect the rest of the study population who may not have used maintenance budesonide as regularly. The

Hawthorne effect describes how a person's behaviour might alter because they are aware they are being studied, however the extent to which the behaviour of participants in a clinical trial alters as a result of being studied is unclear[292]. Because the PRACTICAL study had an open label, real world design, and no placebo inhalers were used, the pattern of behaviour seen in the as-needed budesonide-formoterol group is likely to be representative of how this regimen would be used by patients with mild-moderate asthma in clinical practice.

While an estimate of dose of each inhaler taken could have been obtained from the use of patient diaries, weighing inhalers or from the inhaler dose counter, none of these methods would have provided as accurate data or allowed patterns of use to be explored. Use of electronic inhaler monitors is the only method which allows accurate calculation of dose taken and patterns of use to be explored. In addition, the electronic inhaler monitors we used have an accuracy of 99.9% in measuring inhaler use[215]. Summary outcomes for the electronic inhaler monitor dispensed to a patient are presented Appendix 8.5. Of the 816 monitors dispensed across the whole study only six monitors were lost by participants and 16 were broken. Therefore, data was lost from 22 monitors, 2.7% of all monitors dispensed, representing only a very small fraction of the total data set, so the results are representative of the electronic monitoring sub-study.

3.5.2. Future work

The Novel START and SYGMA studies have a wealth of data obtained from electronic inhaler monitors from a larger population than in the PRACTICAL study. These databases could be used to further investigate the patterns of as-needed budesonide-formoterol use in comparison with maintenance budesonide plus SABA reliever therapy. The considerably larger populations in these studies provides the opportunity to investigate other hypothesis such as the differing association between as-needed beta$_2$-agonist use and risk of severe exacerbations depending on whether the beta$_2$-agonist is taken alone or in combination with ICS. Preliminary analyses from the SYGMA 1 study reported in a conference abstract[293] showed that increased use of

SABA either alone or in combination with maintenance ICS therapy was associated with increased risk of severe exacerbations in the next 21 days. Whereas, use of a beta$_2$-agonist with ICS in the form of as-needed budesonide-formoterol was not associated with increased risk. These findings indicate SABA reliever therapy is a predictor of severe exacerbation risk and use of budesonide-formoterol as reliever therapy modifies the risk, presumably through increased use of ICS component. The inclusion of SABA alone as a randomised treatment in the Novel START and SYGMA 1 studies also allows patters of budesonide-formoterol reliever therapy to be compared with patterns of SABA reliever therapy either in addition to maintenance ICS (all four studies) or alone. Finally, these data sets could be examined to determine if there are patterns of inhaler use that are predictive of asthma exacerbations and if they differ depending on type of reliever therapy used, thus providing an early warning system.

3.6. Conclusion

In conclusion the electronic monitoring sub-study has shown in patients with mild-moderate asthma use of as-needed budesonide-formoterol resulted in a lower rate of severe exacerbations with similar control of asthma symptoms at a significantly lower exposure to ICS than use of maintenance budesonide plus as-needed terbutaline. In the budesonide-formoterol group prolonged periods of no ICS use coupled with periods of increased use suggest the mechanism for how as-needed budesonide-formoterol achieves its clinical effects at a significantly lower exposure to ICS is through titration of ICS via the vehicle of a bronchodilator and timing of ICS is more important than total dose taken. Patients take less ICS when well and more when asthma is worsening. Use of maintenance ICS is likely to lead to times when the patient takes more ICS than required, and other times such as during worsening asthma when insufficient ICS is taken. It is likely that the use of formoterol instead of a SABA also contributes the reduction in severe exacerbation rate.

4. The Preferences Survey

4.1. Introduction

The PRACTICAL study and the electronic monitoring sub-study found symptom-driven budesonide-formoterol was an effective and safe alternative to maintenance budesonide plus terbutaline as needed, which reduces risk of severe asthma exacerbations at a significantly lower exposure to ICS through up-titrating use of budesonide-formoterol in response to symptoms. From a medical perspective, symptom-driven ICS-formoterol is an attractive regimen in mild-moderate asthma as it has the potential to circumvent the problems of SABA overuse and ICS underuse during periods of asthma worsening[100,112]. However patient perspectives on and preferences for symptom-driven budesonide-formoterol are fundamental when considering if this new treatment strategy is appropriate for patients with mild-moderate asthma.

Symptom-driven treatment may align more closely with patients' preferences as it is less intrusive, and patients' have more control over this regimen[119,139,242]. However, because as-needed budesonide-formoterol is a novel regimen there is no data on patient preferences for or experiences of using this regimen to control asthma. During their study visits, participants in the PRACTICAL study often spontaneously offered their opinions and views on their asthma treatment particularly if they were randomised to as-needed budesonide-formoterol. During the study it was unclear which treatment would be superior, so knowledge of patient preferences for the two regimens was felt to be important particularly if both maintenance and as-needed treatment were found to be equivalent. Therefore, a survey exploring patient preferences, beliefs, satisfaction, reported patterns of reliever use and experience with respect to the two asthma treatment regimens used in the PRACTICAL study was developed. This chapter addresses the third aim of this thesis.

The preferences survey was published in The European Respiratory Journal in January 2020[294]. As an author of the published article I retain the right to include it in a thesis or dissertation, provided it is not published commercially. Permission is not required.

4.2. Aims

The primary aim was to determine if participants had a preference for either symptom-driven ICS or daily maintenance ICS.

Secondary aims were:

i. To explore patient preferences for preventer inhaler use

ii. To explore patient beliefs around preventer inhaler use

iii. To explore satisfaction with study inhalers

iv. To explore patient reported patters of reliever inhaler use

v. To explore experience of using symptom-driven budesonide-formoterol

4.3. Methods

4.3.1. Survey design

The survey was nested within the PRACTICAL study. Survey design was informed by the study aims and review of the literature around patterns of inhaler use, adherence, beliefs about medicines, and preferences for asthma treatments and management. This body of literature was discussed in the Introduction. The full survey is given in Table 23. Where relevant some questions that had previously been used in the literature were incorporated, these are referenced. The survey was divided into six themes aligned to the primary and secondary aims.

- Theme one: preferences for preventer inhaler use
- Theme two: beliefs around preventer inhaler use
- Theme three: patterns of study reliever inhaler use

- Theme four: satisfaction with study inhalers
- Theme five: experience of using as-needed budesonide-formoterol
- Theme six: overall regimen preference

Responses to questions on themes one to five were recorded on a 5 point Likert scale, response to the question on overall regimen preference was a dichotomous choice between the two treatment regimens used in the PRACTICAL study. The survey was pilot tested on 11 people who had already completed the PRACTICAL study to check ease of understanding, relevance of the questions and cognitive burden. Cognitive debriefing techniques were used to enhance feedback on the survey and iterative changes based on the feedback were made to improve the relevance of questions and ease of understanding.

Table 23: Full preferences survey

Question themes: preferences around preventer inhaler use (theme 1) and beliefs about preventer inhaler use (theme 2).

Question Theme	Following are some questions about your asthma and asthma treatment. Please put a tick in the box which is closest to how you feel.	Strongly Disagree	Disagree	Uncertain	Agree	Strongly Agree
2	When I feel well, I believe there is no need to take a preventer inhaler every day.[100]					
2	I am willing to accept having asthma symptoms more often if it means I don't have to take a preventer inhaler every day.					
1	I would prefer not to take a preventer inhaler every day if I don't have asthma symptoms.					
2	I am concerned about taking too much medication when I am well.[100]					
1	I would prefer to adjust the amount of my preventer inhaler to the changes in my asthma, taking less when feeling well and more when feeling worse.[100]					
1	I would prefer to take a preventer inhaler every day to try and avoid as many symptoms as possible.[100] *					
1	I would prefer all my asthma medications to be combined into one inhaler.					
2	I am confident I know my asthma well enough to intervene early to try and prevent worsening symptoms.[295]					
2	I consider it normal for me to get symptoms of asthma.					

* Question "I would prefer to take a preventer inhaler every day to try and avoid as many symptoms as possible": the direction of response is opposite to the other questions. If a participant agreed they are indicating they would prefer maintenance treatment, whereas for the other questions above agreement indicates a preference for symptom-driven treatment.

Question themes: Patterns of study reliever inhaler use (theme 3) and experience of using budesonide-formoterol reliever regimen theme (theme 5).

Question Theme	Following are some questions about your asthma and asthma treatment. Please put a tick in the box which corresponds best to what you felt or did during the study.	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
3	During the study sometimes I found it difficult to know if a symptom was due to asthma or not					
3	During the study I took my reliever as soon as I got mild asthma symptoms					
3	During the study I waited until asthma symptoms were having an impact on what I was doing before I took my reliever inhaler					
3	During the study I tried to wait as long as possible before I took my reliever inhaler					
3	During the study I tried to avoid taking my reliever inhaler as much as possible					
3	During the study there were times when I felt I should have taken the reliever inhaler but didn't					
5	During the study I would have preferred to take a regular preventer inhaler to stop me getting asthma symptoms¥					
3	I usually took my reliever before or during exercise					
3	I always carried my reliever inhaler with me					

¥ Question asked to budesonide-formoterol arm only

Question theme: Satisfaction with study inhalers (theme 4).

Question Theme	Thinking about how satisfied you were with the budesonide-formoterol inhaler you were on for the study please put a tick in the box which is closest to how you feel.[236]¥	Very dissatisfied	Dissatisfied	Uncertain	Satisfied	Very satisfied
4	Effectiveness (how well it worked for me)					
4	How fast it acted					
4	How often I needed to take it					

¥ Question asked to budesonide-formoterol arm only

Question Theme	Thinking about how satisfied you were with the budesonide inhaler you were on for the study please put a tick in the box which is closest to how you feel.[236]±	Very dissatisfied	Dissatisfied	Uncertain	Satisfied	Very satisfied
4	Effectiveness (how well it worked for me)					
4	How often I needed to take it					

±Questions asked to maintenance budesonide arm only

Did you use the Bricanyl inhaler during the study? (Following questions on Bricanyl not shown if no selected)±

i. Yes/No

Question Theme	**Thinking about how satisfied you were with the terbutaline inhaler you were on for the study please put a tick in the box which is closest to how you feel.**[236]**±**	**Very dissatisfied**	**Dissatisfied**	**Uncertain**	**Satisfied**	**Very satisfied**
4	Effectiveness (how well it worked for me)					
4	How fast it acted					
4	How often I needed to take it					

±Questions asked to maintenance budesonide arm only

Question theme: Experience of using the budesonide-formoterol reliever regimen (theme 5)

Questions asked to budesonide-formoterol arm only:

Question Theme	**Thinking about using budesonide-formoterol as a reliever during the study, please put a tick in the box which you feels best corresponds to how you feel.**	**Very unconfident**	**Unconfident**	**Uncertain**	**Confident**	**Very confident**
5	How confident were you in using budesonide formoterol as a reliever inhaler at the start of the study?					
5	How confident were you in using budesonide-formoterol as a reliever inhaler at the end of the study?					
5	I was apprehensive about not taking the reliever inhaler I was on before the study (e.g. Ventolin) any more	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
5	Compared to the reliever inhaler I was on before the study, I felt that when I took a puff of the budesonide-formoterol inhaler, it worked:	A lot slower	A bit slower	About the same	A bit faster	A lot faster
5	Compared to the reliever inhaler I was on before the study, I felt the length of time the budesonide-formoterol inhaler worked for after I took a puff was:	A lot shorter	A bit shorter	About the same	A bit longer	A lot longer

Question theme: overall regimen preference (theme 6).

Regimen preference

Which of the following asthma treatment plans would you prefer?

1. A preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed
2. A combined preventer and reliever inhaler taken as needed

4.3.2. Participants

This was a sub-study nested within the PRACTICAL study. Participants at six of the 15 sites who were due their final study visit on or after 26 March 2018 were eligible to undertake the survey. This date was chosen as the preferences survey was developed during the PRACTICAL study. If a participant had withdrawn from the study early but would have otherwise been eligible they were contacted and asked if they would return to complete the survey retrospectively.

4.3.3. Survey delivery

Unless a participant was returning to complete the survey retrospectively, the survey was completed at the final study visit. All participants provided separate written consent to undertake the survey. The patient information and consent sheet is provided in Appendix 8.6. Prior to starting the survey, participants were asked to read an information sheet explaining what the terms preventer and reliever meant and reminding them of the two regimens used in the PRACTICAL study. The information sheet is given in Figure 25. The survey data were collected and managed using REDCap electronic data capture tools hosted at Medical Research Institute of New Zealand[296,297]. The participants self-completed the survey online in the same room as an investigator.

Explanation of Terms in the Survey

Reliever inhaler: used when you are getting symptoms of asthma such as breathlessness, wheeze, tight-chested or cough. You may have been on a Ventolin or Respigen inhaler as your reliever before the study. In the study you would have used either Bricanyl (blue) or Symbicort (red) inhaler as your reliever inhaler.

Preventer inhaler: contains a corticosteroid to reduce inflammation. This type of inhaler is normally used regularly twice a day to prevent asthma symptoms and reduce the risk of flare-ups. In the study you may have been using Pulmicort (brown) inhaler twice a day as your preventer. Other preventer inhalers you may have taken before the study are Beclazone (brown) or Flixotide (orange).

Combined preventer and reliever inhaler: In the study, you may have been using Symbicort (red) as a combined preventer and reliever when you had asthma symptoms.

The different inhaler regimens in the study:

Regimen	**What inhalers are given and why?**	**When would I take the inhaler(s)?**	
Symbicort	Symbicort inhaler Combined preventer and reliever This contains: - a beta- agonist to quickly open up the airways - a steroid to reduce airway inflammation	When I have symptoms	
Pulmicort and Bricanyl	Bricanyl inhaler Reliever inhaler This contains a beta- agonist to quickly open up the airways	When I have symptoms	
	Pulmicort inhaler Preventer inhaler This contains a steroid to reduce airway inflammation	Morning and night	

Figure 25: Participant explanation of terms in the preferences survey sheet

4.3.4. Outcomes

The primary outcome was description of the proportions of participants choosing each treatment (either a combined preventer and reliever inhaler taken as needed or a preventer inhaler taken twice a day every day with a reliever inhaler taken as needed). With a sensitivity analysis to test if treatment preference was modified by randomised treatment or use of ICS at study entry.

Secondary outcomes were:

- Frequency distribution of answers for all five points on the Likert scales for questions exploring themes one to five (preferences for preventer inhaler use; beliefs around preventer inhaler use; patterns of study reliever inhaler use; satisfaction with study inhalers; experience of using as-needed budesonide-formoterol).
- Sensitivity analyses to test if response on five point Likert scale was modified by randomised treatment or use of ICS or not at study entry (questions on themes one to four only).

4.3.5. Statistical analysis

Continuous variables are described by mean and SD, and median and IQR. Categorical variables are described by counts and proportions expressed as percentages. Ordinal variables are described using a label of 1 to 5 reflecting the ordinal Likert variable response. Preference for treatment regimen by randomised treatment was analysed by logistic regression, a higher odds ratio reflects that those randomised to as-needed budesonide-formoterol were more likely to have a preference for combination treatment as needed with an interaction term to test if stated preference differed by ICS use at baseline. For questions covering theme one to four the extent of agreement as indicated by a higher Likert score were analysed by logistic regression where a higher odds ratio favours association between agreement and randomisation to as-needed budesonide-formoterol. Interaction terms tested if this association differed by

ICS use at baseline. SAS version 9.4 (SAS Institute Inc., Cary, USA) was used for all analyses.

4.4. Results

407 participants were due to finish the PRACTICAL study on or after 26 March 2018 at the six participating sites and were therefore eligible for the survey. 307/407 (75%) participants started the survey, one person started the survey but did not complete it. The characteristics of participants who started the survey and of participants who were eligible to undertake the survey but did not are shown in Table 24. Proportions of participants in both randomised treatment arms were similar among those who did and did not start the survey. At baseline, participants who started the survey were on average 15 years older, were 10 years older at diagnosis, and had higher self-reported adherence to ICS pre study. End of study outcomes in those who didn't start the survey showed they had a higher FeNO and a slightly higher ACQ-5, and early withdrawal rate was far greater in those who didn't start the survey than in those who did (56% versus 7%). Reasons for not completing the survey are shown in Table 25, and were similar in both treatment arms.

Table 24: Characteristics of participants eligible for preferences survey

Characteristic	Survey not started (n=100)	Survey started (n=307)
Randomised treatment		
Budesonide-formoterol no.(%)	52 (52)	151 (49)
Maintenance budesonide no.(%)	48 (48)	156 (51)
Baseline variables		
Age (years)	30.1 (10.6)	45.9 (16)
Age at diagnosis (years)	11.2 (10.7)	21.1 (19.3)
Female sex no.(%)	50 (50)	172 (56)
Ethnicity no.(%)		
Asian	10 (10)	17 (6)
NZ European	67 (67)	247 (81)
Māori	11 (11)	24 (8)
Other	4 (4)	5 (2)
Pacific	8 (8)	14 (5)
Smoking status no.(%)		
Current smokers	9 (9)	14 (5)
Ex-smokers	28 (28)	77 (26)
Never smokers	63 (63)	214 (70)
Pack years (ever smokers)	3.5 (3.6)	5.4 (5.0)
ICS use ever no.(%)	71 (71)	264 (86)
ICS use at randomisation no.(%)*	66 (66)	215 (70)
Self-reported ICS adherence (%)¥	40.5 (32.8) (n=66)	57.0 (35.9) (n=215)
Weekly occasions of SABA use	4.0 (4.0)	4.0 (5.2)
Participants with ≥1 hospital admission for asthma ever no.(%)	18 (18)	40 (13)
One or more severe exacerbation in the preceding 12 months no.(%)	14 (14)	28 (9)
End of study variables		
Final visit ACQ-5†	0.97 (0.88) (n=56)	0.78 (0.72)
Final visit on treatment FEV_1 % of predicted value‡	88.3 (15.9) (n=54)	89.2 (14.8)
Final visit median FeNO – ppb (IQR)	40.5 (28 to 58) (n=54)	23 (15 to 40)
Participants experiencing ≥1 exacerbation or severe exacerbation during the study no.(%)	14 (14)	34 (11)
Early withdrawal no.(%)	56 (56)	20 (7)

Values are expressed as means (SD) or median (IQR) unless otherwise indicated

* Participants self-reported ICS use in the 12 weeks prior to randomisation

¥ Participant self-reported adherence to ICS in the 4 weeks prior to enrolment (% prescribed dose).

† The Asthma Control Questionnaire–5 (ACQ-5) consists of five questions that assess asthma symptoms in the previous week

Table 25: Reasons the preferences survey was not completed

Reason – no.(%)	Budesonide-formoterol as needed N=53	Maintenance budesonide N=48
Did not provide consent	25 (47)	22 (46)
Withdrawn at randomisation visit due to safety concerns	0	1 (2)
Early withdrawal prior to 26 March 2018 and did not return to complete survey retrospectively	5 (9)	7 (15)
Early withdrawal and did not attend for final study visit	7 (13)	6 (13)
Lost to follow up	15 (28)	12 (25)
Started survey but did not complete it	1 (2)	0

4.4.1. Primary outcome

A combined preventer and reliever inhaler taken as needed was the preferred regimen over a preventer inhaler taken twice a day with a reliever inhaler taken as needed. 198/306 participants preferred as-needed treatment (65%, 95%CI 59.4 to 70.1) versus 108/306 participants who preferred maintenance treatment (35%). Of those randomised to as-needed budesonide-formoterol, as-needed treatment was preferred by 135/150 (90%, 95%CI 85.2 to 94.8) of participants and maintenance treatment was preferred by 15/150 (10%). Of those randomised to maintenance budesonide, as-needed treatment was preferred by 63/156 (40%, 95%CI 32.7 to 48.1) and maintenance treatment was preferred by 93/156 (60%). Treatment preference by randomised treatment is shown in Table 26. Odds ratio for association between randomised treatment and preference for as needed treatment was 13.3 (95%CI 7.1 to 24.7), $p<0.001$. Indicating that randomisation to as-needed budesonide-formoterol was very strongly associated with preference for as-needed treatment. Following adjustment for baseline ICS use the odds ratio was 13.6 (95%CI 7.3 to 25.5), $p<0.001$ indicating that the association was not affected by use of ICS at baseline.

Characteristics of participants by randomised treatment arm and preferred regimen were similar, except proportion of participants who withdrew from the study early was higher in those who were randomised to as-needed budesonide-formoterol but preferred maintenance treatment (Table 27).

Table 26: Asthma regimen preference

Randomised treatment	Preferred treatment, n (%)			
	Combined preventer and reliever inhaler taken as needed	Preventer inhaler taken twice a day with a reliever inhaler as needed	Odds ratio & 95%CI preference for combined vs regular treatment	P
Budesonide-formoterol n=150	135 (90)	15 (10)		
Maintenance budesonide n=156	63 (40)	93 (60)		
Total n=306	198 (65)	108 (35)	13.3 (7.1 to 24.7)	<0.001
After adjustment for baseline ICS use			13.6 (7.3 to 25.5)	<0.001

Table 27: Participant characteristics by randomised treatment and regimen preference

Randomised treatment	**Budesonide-formoterol as needed**		**Maintenance budesonide plus as-needed terbutaline**	
Regimen Preference	Combined preventer and reliever inhaler taken as needed	Preventer inhaler taken twice a day with a reliever inhaler as needed	Combined preventer and reliever inhaler taken as needed	Preventer inhaler taken twice a day with a reliever inhaler as needed
Number	135	15	63	93
Age – years	45.6 (14.5)	44.1 (23.2)	41.8 (16.1)	47.7 (17.1)
Age at diagnosis – years	19.7 (17.9)	23.9 (26.9)	18.7 (18.7)	24.1 (20.1)
Female sex no. (%)	78 (58)	10 (67)	33 (52)	50 (54)
Ever smoker (%)	42 (31)	4 (27)	20 (32)	26 (28)
Pack years (among ever smokers)	5.2 (4.3)	5.8 (7.8)	6.5 (5.9)	5.2 (5.2)
Use of ICS ever no. (%)	119 (88)	14 (93)	51 (81)	80 (86)
Use of ICS at randomisation* no. (%)	93 (69)	11 (73)	39 (62)	72 (77)
Adherence to ICS (% of prescribed dose)¥	53.1 (36.7)	67.5 (33.3)	53.3 (38.2)	62.6 (33.7)
Weekly occasions of SABA use	3.9 (5.1)	4.4 (5.9)	4.2 (4.9)	3.9 (5.5)
Final visit ACQ-5†	0.84 (0.64)	1.00 (0.76)	0.82 (0.84)	0.62 (0.73)
Final visit FEV_1 % of predicted value	89.5 (14.8)	92.6 (17.6)	89.7 (14.4)	88.0 (14.9)
Final visit FeNO – ppb (IQR)	22 (15 to 38.5)	22 (15 to 47.5)	22 (13 to 36.5)	23 (15 to 40)
Participants with ≥1 exacerbation during the study no. (%)	16 (12)	1 (7)	12 (19)	18 (19)
Early withdrawal no. (%)	3 (2)	4 (27)	6 (10)	7 (8)

Values are expressed as means (SD) or median (IQR) unless otherwise indicated

* Participants self-reported ICS use in the 12 weeks prior to randomisation

¥ Participant self-reported adherence to ICS in the 4 weeks prior to enrolment (% prescribed dose)

† The Asthma Control Questionnaire–5 (ACQ-5) consists of five questions that assess asthma symptoms in the previous week

4.4.2. Secondary outcomes

Theme one: preferences for preventer inhaler use

Numbers and proportions of participants who chose strongly disagree/disagree, uncertain or agree/strongly agree are given in Table 28. Participants randomised to as-needed budesonide-formoterol were more likely to prefer not to take an inhaler every day, express a preference for being able to adjust dosing, and for all asthma medications to be combined into a single inhaler. There was strong evidence of variation in response by randomisation arm, and these effects were not modified by use of ICS at study entry. Odds ratios all indicated that participants were significantly more likely to agree/strongly agree with the question if randomised to as-needed budesonide-formoterol.

Theme two: beliefs around preventer inhaler use

Participants randomised to as-needed budesonide-formoterol were more likely to believe a daily preventer was not necessary when well, have concerns about taking too much medication when well, consider it normal to get asthma symptoms and have confidence in being able to intervene when asthma symptoms were worsening (Table 29). There was no evidence of effect modification from use of ICS at study entry. While more participants randomised to as-needed budesonide-formoterol were willing to accept more asthma symptoms to avoid taking a daily preventer, numbers expressing agreement with this statement were low. Odds ratios all indicated that participants were significantly more likely to agree/strongly agree with the question if randomised to as-needed budesonide-formoterol.

Theme three: patterns of study reliever inhaler use

Most participants agreed they always carried their reliever inhaler with them and took their reliever inhaler as soon as they got mild symptoms. However, in both randomised groups around one third waited until asthma was having an impact on what they were doing and almost 20% tried to avoid taking their reliever inhalers as much as possible. Approximately 30% admitted difficulty in recognising asthma

symptoms. Numbers and proportions of participants who chose strongly disagree/disagree, uncertain or agree/strongly agree to questions on patterns of reliever inhaler use are given in Table 30. For this set of statements there was no association with randomised treatment as indicated by odds ratios of the order of one with non-significant p values.

Theme four: satisfaction with study inhalers

Numbers and proportions of participants who were very dissatisfied/dissatisfied, uncertain or satisfied/very satisfied with the effectiveness, frequency of use and speed of action (reliever inhaler only) of each of their study inhalers is given in Table 31. Overall satisfaction was high for all study inhalers for each of the three domains however, odds ratios suggested that participants were more likely to rate being satisfied or very satisfied in all three domains if they had been using the budesonide-formoterol inhaler than either the terbutaline or budesonide inhalers.

Theme five: experience of using as-needed budesonide-formoterol

The patterns of response to questions on experiences of using as-needed budesonide-formoterol are given in Table 32. Among participants randomised to as-needed budesonide-formoterol 32/151 (21%) agreed/strongly agreed they would have preferred to take a regular preventer inhaler to stop them getting asthma symptoms and 102/151 (68%) disagreed/strongly disagreed. Over one third, 55/150 (37%) agreed/strongly agreed had been apprehensive about not taking their usual reliever inhaler any more. 111/150 (74%) felt confident in using budesonide-formoterol as a reliever inhaler at the start of the study and 138/150 (92%) felt confident with using budesonide-formoterol as reliever inhaler by the end of the study. Approximately one third felt the onset of budesonide-formoterol was faster than their previous reliever inhalers, one third were uncertain and one third felt onset was slower than their previous reliever. In all 66/150 (44%) felt the duration of relief from budesonide-formoterol was longer than their previous reliever inhalers.

Table 28: Response to questions on preference for preventer inhaler use

Randomised treatment	Budesonide-formoterol n=151, N(%)			Maintenance budesonide n=156, N(%)			±Odds ratio & 95%CI	P
	Strongly disagree/ disagree	Uncertain	Agree/ strongly agree	Strongly disagree/ disagree	Uncertain	Agree/ strongly agree		
I would prefer not to take a preventer inhaler every day if I don't have asthma symptoms	20 (13)	16 (11)	115 (76)	53 (34)	21 (13)	82 (53)	2.98 (1.93 to 4.59)	<0.001
I would prefer to take a preventer inhaler every day to try and avoid as many symptoms as possible¥[100]	62 (41)	25 (17)	64 (42)	26 (17)	23 (15)	107 (69)	3.01 (1.96 to 4.60)	<0.001
I would prefer to adjust the amount of my preventer inhaler to the changes in my asthma taking less when feeling well and more when feeling worse[100]	27 (18)	18 (12)	106 (70)	56 (36)	28 (18)	72 (46)	2.62 (1.71 to 4.0)	<0.001
I would prefer all my asthma medications to be combined into one inhaler	10 (7)	15 (10)	126 (83)	41 (26)	46 (30)	69 (44)	6.29 (3.99 to 9.93)	<0.001

±Odds ratio greater than one indicates survey respondents were more likely to agree with the statement if randomised to as-needed budesonide-formoterol than if randomised to maintenance budesonide

¥Direction of response was in the opposite direction to all other questions, this was accounted for in the analysis

Table 29: Response to questions on beliefs around preventer inhalers

Randomised treatment	Budesonide-formoterol N=151; N (%)			Maintenance budesonide N=156; N (%)			±Odds ratio & 95%CI	P
	Strongly disagree/ disagree	Uncertain	Agree/ strongly agree	Strongly disagree/ disagree	Uncertain	Agree/ strongly agree		
I am confident I know my asthma well enough to intervene early to try and prevent worsening symptoms[295]	4 (3)	15 (10)	132 (87)	13 (8)	18 (12)	125 (80)	1.89 (1.21 to 2.94)	0.005
I consider it normal for me to get symptoms of asthma	29 (19)	15 (10)	107 (71)	43 (28)	14 (9)	99 (63)	1.59 (1.03 to 2.48)	0.039
When I feel well, I believe there is no need to take a preventer inhaler every day[100]	41 (27)	15 (10)	95 (63)	98 (63)	8 (5)	50 (32)	3.94 (2.57 to 6.04)	<0.001
I am willing to accept having asthma symptoms more often if it means I don't have to take a preventer inhaler every day	86 (57)	23 (15)	42 (28)	116 (74)	19 (12)	21 (13)	2.58 (1.69 to 3.94)	<0.001
I am concerned about taking too much medication when I am well[100]	52 (34)	26 (17)	73 (48)	77 (49)	29 (19)	50 (32)	1.85 (1.23 to 2.78)	0.003

±Odds ratio greater than one indicates survey respondents were more likely to agree with the statement if randomised to as-needed budesonide-formoterol than if randomised to maintenance budesonide

Table 30: Response to questions on patters of reliever inhaler use

Randomised treatment	Budesonide-formoterol N=151; N (%)			Maintenance budesonide N=156; N (%)			±Odds ratio & 95%CI	P
	Strongly disagree/ disagree	Uncertain	Agree/ strongly agree	Strongly disagree/ disagree	Uncertain	Agree/strongly agree		
I always carried my reliever inhaler with me	31 (21)	3 (2)	117 (77)	50 (32)	4 (3)	102 (65)	1.67 (1.10 to 2.53)	0.016
Sometimes I found it difficult to know if a symptom was due to asthma or not	87 (58)	20 (13)	43 (28)	91 (58)	16 (10)	49 (31)	1.03 (0.68 to 1.57)	0.89
I took my reliever as soon as I got mild asthma symptoms	33 (22)	18 (12)	100 (66)	45 (29)	10 (6)	101 (65)	1.25 (0.81 to 1.94)	0.31
I waited until asthma symptoms were having an impact on what I was doing before I took my reliever inhaler	90 (59)	7 (5)	54 (36)	88 (56)	10 (6)	58 (37)	1.01 (0.66 to 1.53)	0.98
I tried to wait as long as possible before I took my reliever inhaler	116 (77)	9 (6)	26 (17)	125 (80)	6 (4)	25 (16)	1.36 (0.87 to 2.15)	0.18
I tried to avoid taking my reliever inhaler as much as possible	116 (77)	8 (5)	27 (18)	119 (76)	10 (6)	27 (17)	0.97 (0.62 to 1.51)	0.88
There were times when I felt I should have taken the reliever inhaler but didn't	77 (51)	13 (9)	61 (40)	101 (65)	11 (7)	44 (28)	1.67 (1.10 to 2.54)	0.017
I usually took my reliever before or during exercise	62 (41)	18 (12)	71 (47)	89 (57)	9 (6)	58 (37)	1.61 (1.07 to 2.43)	0.024

±Odds ratio greater than one indicates survey respondents were more likely to agree with the statement if randomised to as-needed budesonide-formoterol than if randomised to maintenance budesonide

Table 31: Satisfaction with study inhalers

Inhaler	Budesonide-formoterol inhaler N=151; N (%)			Terbutaline inhaler N=147¥; N (%)			Budesonide inhaler N=156; N (%)			±Odds ratio & 95%CI budesonide formoterol vs terbutaline	±Odds ratio & 95%CI budesonide formoterol vs budesonide
	Very unsatisfied/ unsatisfied	Uncertain	Satisfied/ very satisfied	Very unsatisfied/ unsatisfied	Uncertain	Satisfied/ very satisfied	Very unsatisfied/ unsatisfied	Uncertain	Satisfied/ very satisfied		
Inhaler effectiveness[236]	7 (5)	4 (3)	140 (93)	6 (4)	14 (10)	127 (86)	6 (4)	15 (10)	135 (86)	2.74 (1.74 to 4.29) p<0.001	2.37 (1.53 to 3.68) p<0.001
Frequency of inhaler use[236]	9 (6)	8 (5)	134 (89)	5 (3)	18 (12)	124 (84)	13 (8)	21 (14)	122 (78)	1.90 (1.21 to 2.97) p=0.005	2.26 (1.46 to 3.51) 0<0.001
Inhaler speed of action[236]α	12 (8)	10 (7)	129 (85)	11 (8)	21 (14)	115 (78)	---	---	---	1.56 (1.01 to 2.41) p=0.044	---

±Odds ratio greater than one indicates survey respondents were more likely to agree with the statement if randomised to as-needed budesonide-formoterol than if randomised to maintenance budesonide

¥Participants randomised to maintenance budesonide only saw questions on the terbutaline inhaler if they answered yes to using the inhaler during the study. Nine patients answered no

α Question only asked regarding budesonide-formoterol and terbutaline inhalers

Table 32: Experience of using budesonide-formoterol as a symptom-driven preventer and reliever

	Agree/strongly agree	**Uncertain**	**Disagree/strongly disagree**
I would have preferred to take a regular preventer inhaler to stop me getting asthma symptoms n=151 no.(%)	32 (21)	17 (11)	102 (68)
I was apprehensive about not taking the reliever inhaler I was on before the study any more n=150 no.(%)	55 (37)	20 (13)	75 (50)
	Confident/very confident	Uncertain	Unconfident/very unconfident
Confidence in using budesonide-formoterol as a reliever inhaler at the start of the study n=150	111 (74)	28 (19)	11 (7)
Confidence in using budesonide-formoterol as a reliever inhaler at the end of the study n=150 no.(%)	138 (92)	5 (3)	7 (5)
	A bit/a lot faster	About the same	A bit/a lot slower
Compared to the reliever inhaler I was on before the study, I felt that when I took the budesonide-formoterol inhaler, it worked: no.(%)	58 (39)	43 (29)	49 (33)
	A bit/a lot longer	About the same	A bit/a lot shorter
Compared to the reliever inhaler I was on before the study, I felt the length of time the budesonide-formoterol inhaler worked for after I took a puff was: no.(%)	66 (44)	60 (40)	24 (16)

4.5. Discussion

The preferences survey found most participants preferred their randomised treatment. This was particularly striking for those randomised to as-needed budesonide-formoterol, in whom 90% preferred a combined inhaler taken as needed and only 10% preferred a preventer inhaler taken twice a day. In those randomised to maintenance budesonide 40% preferred the combined inhaler taken as needed and 60% preferred the regimen that corresponded to their randomised treatment – a preventer inhaler twice daily. Odds ratios confirm the regimen that participants preferred was strongly associated with randomised treatment, use of maintenance ICS at study entry did not affect regimen preference. These results suggest once a patient has tried combination therapy as needed, it is likely they will prefer it to maintenance treatment. This provides evidence that use of symptom-driven budesonide-formoterol as an acceptable alternative management strategy to patients with mild-moderate asthma. Patients who have not experienced as-needed budesonide-formoterol may be more cautious about taking symptom-driven therapy. Therefore, patients may only be able to make an informed decision after a trial of symptom-driven therapy.

Response to questions on preferences for and beliefs about preventer inhaler use were also affected by randomised treatment. Participants randomised to as-needed budesonide-formoterol were more likely to agree to questions on preference for and beliefs about preventer inhalers that reflected the symptom-driven regimen such as combination of all medications in one inhaler, flexible dosing titrated to symptoms, or no daily commitment. This corresponded with their overall preference for as-needed therapy. Participants randomised to maintenance budesonide, who had not experienced as-needed treatment were more divided in their responses. The results of the preferences survey complement the literature (discussed in the Introduction) that patients with asthma do not want to take maintenance treatment every day. They want a flexible, easy to use regimen that they are in control of[237,240,242], prefer to increase their use of reliever medication over preventer medication in response to worsening asthma[131], and have concerns regarding the use of regular ICS[118,242].

Participants randomised to as-needed budesonide-formoterol and maintenance budesonide had similar patterns of response to questions on reliever inhaler use. This indicates that randomised treatment did not affect their behaviour with respect to how they used reliever inhalers. It is likely that for budesonide-formoterol reliever therapy to be safe and effective, patients would need to take their inhaler in response to symptoms and not delay or avoid using it. We found that some patients admitted having difficulty recognising if a symptom was due to asthma or avoided or delayed taking their reliever inhalers. It is reassuring that they were in the minority with similar numbers and pattern of behaviour in both treatment arms. However, this highlights that identification of symptoms and appropriate use of reliever inhalers should be considered particularly when starting a patient on as-needed budesonide-formoterol, and they should be provided with appropriate education around asthma symptoms and when to use their inhalers.

Most participants reported they were satisfied with their study inhalers' effectiveness, speed of onset and frequency of use. However, those randomised to as needed-budesonide formoterol were more likely to report higher levels of satisfaction with the budesonide-formoterol inhaler than those who were randomised to maintenance budesonide were with the budesonide or terbutaline inhalers.

Most participants randomised to as-needed budesonide-formoterol rated their experience of using this treatment favourably. 37% had been apprehensive about not taking the reliever inhaler they were on before the study anymore and 74% of participants stated they were confident using budesonide-formoterol as reliever at the start of the study. This number increased to 92% when asked about their confidence using budesonide-formoterol as a reliever at the end of the study. Only 21% would have preferred to take a regular preventer inhaler to prevent asthma symptoms. Taken together this is reassuring as it suggests if a patient has initial reservations about using as-needed budesonide-formoterol, it is likely they will be confident in using it as a reliever and will prefer it to regular maintenance therapy after a trial of treatment. Approximately one third of participants felt the speed of action of budesonide-formoterol reliever therapy was slower than their previous relievers. The

majority felt that budesonide-formoterol was about the same or faster acting, suggesting that despite formoterol having a slightly slower onset than salbutamol or terbutaline[298], for most participants this was not noticeable.

The findings of the preferences survey suggest that as-needed budesonide-formoterol is a regimen that will be acceptable to patients, and will be preferred to daily maintenance ICS with a reliever as required. This complements the findings of the PRACTICAL study and the Novel START and SGYMA 1 & 2 studies that as-needed budesonide-formoterol is a safe and effective alternative to daily maintenance ICS with reliever therapy as required[176–178,279].

4.5.1. Strengths and weaknesses

Weakness of the preferences survey are that 100 eligible participants did not complete the survey. Comparison of their baseline demographics suggests that they may be different from those who did. Participants who withdraw early from an RCT are more likely to be non-responders[299], and it is possible that their answers and preferences may have been different from those who did complete the survey. This may affect the representativeness of the results, however, there was a similar non-completion rate between the two treatment arms.

The survey was conducted in patients finishing an RCT which may affect the generalisability of the results, as the preferences of patients in the general population may be different from those who are willing to take part in an RCT for a year. Among participants in the PRACTICAL study, symptom-driven preventer reliever therapy was preferred to twice daily preventer therapy with a reliever as required, however, other regimens such as once daily preventer plus as-needed SABA or SMART regimen were not included. Participants were asked to answer some questions on reliever and preventer inhaler use to reflect what they did or felt during the study, so the results for these questions are vulnerable to recall bias. In addition, the results may have been affected by social desirability bias, particularly if the participant felt if they answered a question in a certain way this would reflect badly on them. To limit cognitive burden, no consistency check questions were included. Because surveys

were not excluded if pattern of participant responses suggested central tendency of response (where the middle option is chosen above all others) or straight lining (where the same option is repeated chosen) no checks for these were undertaken.

Strengths of the preferences survey are that it was nested within an RCT and is the first study to report on patient preferences for as-needed budesonide-formoterol. It highlights how information on patient preferences can be incorporated into RCTs. This may aid understanding of the differences between effectiveness and efficacy seen when a treatment moves from a RCT into clinical practice[287], in which factors such as patient preferences and experience of a treatment are likely to play a role.

4.5.2. Future work

Qualitative studies of patient experiences of and preferences for using as-needed ICS-formoterol would provide deeper understanding of patients' preferences and the factors that are motivating them. A survey of patient preferences and experiences of using as-needed ICS-formoterol as it moves into clinical practice would determine if the pattern of preferences observed in the preferences survey are congruent with the wider population of patients with mild asthma. In addition, a survey of patient preferences including other regimens such as once daily maintenance treatment or SMART therapy, and may determine if there are other regimens which patients would prefer when presented with all potential options.

4.6. Conclusion

In conclusion, participants' preference for inhaler regimen was strongly influenced by their randomised treatment, particularly if they had been randomised to as-needed budesonide-formoterol with 90% preferring this regimen to maintenance budesonide. This suggests that patients prefer as-needed budesonide-formoterol to maintenance budesonide and it will be an acceptable regimen to patients as it is rolled out into clinical practice. Because preference for regimen was strongly influenced by participants' randomised treatment, patients may only be able to make an informed decision after a trial of as-needed budesonide-formoterol.

5. Discrete Choice Experiment

5.1. Introduction

The preferences survey demonstrated that participants preferred symptom-driven budesonide-formoterol, especially if they had been randomised to this treatment and had experienced it. However, it did not determine participants' strength of preference for their preferred regimen or investigate preference for regimen in context with other aspects of asthma management. While a patient may have a preference for one regimen over another, the strength of this preference may be weak and other features of asthma management such as exacerbation risk or frequency of symptoms may be of greater importance to them. Information on how different aspects of treatment regimens influence patient preferences, and the strength of patients' preference for their preferred treatment regimen can be determined from conjoint analysis methods such as DCEs. This information could be incorporated into decision making with a patient regarding the most appropriate regimen for them, particularly if used in context with measured characteristics from RCTs of symptom-driven budesonide-formoterol and maintenance ICS plus SABA as needed regimens.

DCEs are a stated preference methodology which determine preferences through a series of trade-offs that the participant answering the survey makes. Therefore, this methodology is suitable to investigate strength of preference for type of asthma regimen in relation to other features (or attributes) of asthma treatment. An overview DCE methodology and the theory underpinning it, and previous DCEs conducted in patients with asthma were discussed in the Introduction. These studies found shortness of breath was the most important symptom to patients, they wanted as few symptoms as possible, asthma exacerbations significantly affected preference and patients preferred having fewer inhalers.

To quantify the strength of patient preference for different aspects of asthma treatment a DCE was designed in conjunction with the preferences survey and addresses the fourth aim of this thesis.

The discrete choice experiment was published in Thorax in July 2020[300]. As an author of the published article I retain the right to include it in a thesis or dissertation, provided it is not published commercially. Permission is not required.

5.2. Aims

The aim of the DCE was to determine the relative importance of attributes associated with the two inhaler regimens used in the PRACTICAL study: as-needed budesonide-formoterol and maintenance budesonide plus terbutaline as needed; in a sub-group of participants completing the PRACTICAL study.

5.3. Methods

5.3.1. Participants

The same subset of participants who were eligible to complete the preferences survey were eligible to undertake the DCE. The DCE was completed at the final study visit following the preferences survey. If a participant had withdrawn early but would otherwise have been eligible they were contacted and asked if they would be willing to complete the preferences survey and DCE retrospectively. In the literature there are several suggested guidelines for sample size calculation for DCEs[301], however because sample size was determined by the number of potentially eligible participants formal calculations were not undertaken, but 407 participants were eligible.

5.3.2. Attributes and levels

Potential attributes and levels were identified from review of the literature. Eleven participants who had completed the PRACTICAL study attended one of three focus groups to explore the most important features of asthma and its management, with particular focus on factors that had been measured within the PRACTICAL study and how the participants may translate them into attributes and levels. To ensure the DCE outputs would be relatable to the PRACTICAL study's outcomes, the chosen attributes and levels had all been measured during the PRACTICAL study and represented key

features of the two treatment regimens used in the PRACTICAL study. The attributes and levels are given in Table 33.

Table 33: DCE attributes and levels

Attribute	Inherent ranking of levels in as-needed-preference DCE	Inherent ranking of levels in maintenance-preference DCE
Type of asthma treatment	A preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed A combined preventer and reliever inhaler, taken as needed	A combined preventer and reliever inhaler, taken as needed A preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed
The dose of your steroid inhaler	Medium Low Very low	Medium Low Very low
Likelihood of a flare up in your asthma severe enough that you need to see a doctor	20 out of 100 people in a year (20%) 10 out of 100 people in a year (10%) 5 out of 100 people in a year (5%)	20 out of 100 people in a year (20%) 10 out of 100 people in a year (10%) 5 out of 100 people in a year (5%)
In an average week you will be short of breath because of asthma	A moderate amount or more A little Not at all	A moderate amount or more A little Not at all

Each attribute's levels are presented in order of their inherent ranking with the lowest-ranked level listed first.

5.3.3. Discrete choice experiment design

There are several potential methods for designing DCEs[264], however I opted to use a DCE methodology based on the PAPRIKA method[302]. PAPRIKA stands for 'Potentially All Pairwise RanKings of all possible Alternatives' and is implemented by 1000minds software (www.1000minds.com)[303]. In most other DCE methodologies only a subset of all possible choice alternatives are presented to participants so attribute and level preference weights are determined through statistical modelling, the most common type being conditional logit or variations of conditional logit[256]. The PAPRIKA method is different as it provides individual preference weights for each participant. The attribute preference weights add to one for the overall survey and for each individual

participant. Therefore, preference for each attribute is relative to preference for all other attributes.

The PAPRIKA method is able to provide individual preference weights as every pairwise combination of attributes and levels are ranked by the participant either explicitly or implicitly through transitivity. To do this the PAPRIKA method requires the levels for each attribute have an inherent ranking. For example, the attribute of ICS dose had the levels of very low, low and medium. Where the level of very low was considered to be the most desirable and therefore had the highest inherent ranking and the level medium was considered to be the least desirable and therefore had the lowest inherent ranking.

In each choice, set participants were presented with a pair of hypothetical asthma treatments which were defined on just two attributes at a time, along with an opt out of "they are equal". For each choice set the participant was confronted with a trade-off between the levels for the two attributes shown and they had to decide which hypothetical treatment they would prefer based on the attributes and levels shown. An example of a choice set is provided in Figure 26. The choice sets are repeated each time with a different combination of attributes and levels. Each time the participant chose one hypothetical treatment with a particular combination of attributes and levels, the 1000minds software identified all other hypothetical treatment pairs that could be implicitly ranked using the principles of transitivity. For example if a participant explicitly chose X over Y, and Y over Z then X versus Z was implicitly ranked via transitivity and was not asked about. Each time a choice was made by the participant this effected the next choice profile the participant was presented with as the PAPRIKA method adapts and will only ever present combinations of attributes and levels that had not already been ranked either explicitly or implicitly through transitivity. This limits the number of choice profiles a participant sees whilst ensuring that all pairwise combinations of possible treatments are ranked. Individual preference weights are derived from the participant's explicit and implicit rankings.

However, the attribute of treatment regimen does not have an inherent ranking as the ranking of the two levels representing the two treatment regimens in the PRACTICAL study of "a combined preventer and reliever inhaler, taken as needed" and "a preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed" depends on which therapy the participant preferred. Therefore, it was necessary to implement two separate DCEs, identical except that the ranking of the two levels for the 'treatment regimen' attribute were reversed, i.e. for participants who stated they preferred the as-needed therapy this regimen was ranked above the maintenance regimen, and vice versa (see Table 33). After each participant indicated their preferred therapy at the end of the preferences survey, they were presented with the appropriate DCE.

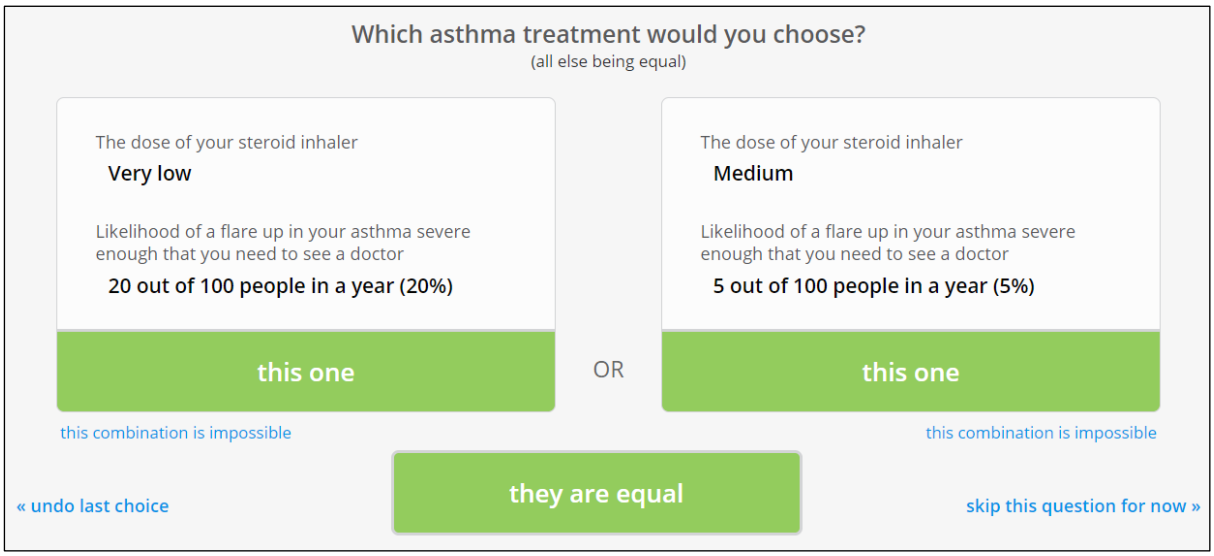

Figure 26: Example DCE choice set

5.3.4. Pilot testing

The same 11 participants who pilot-tested the preferences survey piloted the DCE to check understanding, relevance of selected attributes and levels and time taken to complete the DCE. Cognitive debriefing was used to enhance feedback. Based on their feedback, iterative changes to the wording of the DCE were made to improve understanding. None of the participants found the DCE to be difficult to understand or unduly burdensome.

5.3.5. Data quality checks

The consistency of each participant's choices was tested by repeating two previously answered trade-off questions at the end of the DCE. The time each participant took to answer each question was also recorded by the 1000minds software. Participants who answered both repeated questions inconsistently and/or answered their questions implausibly quickly (less than four seconds per question) were excluded from the final analysis.

5.3.6. Online survey

The DCE was administered via an online self-completed survey delivered by the 1000minds platform. After participants had completed the preferences survey they were automatically directed to either the as-needed preference DCE or the maintenance preference DCE depending on which treatment regimen they had chosen at the end of the preferences survey. In addition to reading the information sheet explaining the terms preventer and reliever inhaler (Figure 25), participants also read an information sheet explaining the DCE, its rationale and how to complete it (Figure 27). The term conjoint survey was used as it was felt this term would be less confusing to participants than the term discrete choice experiment and a DCE is a type of conjoint survey.

Explanation of a Conjoint Survey.

The survey you're going to do next is called a conjoint survey and is slightly different from a usual questionnaire. The purpose of this survey is to find out what is important to you from the various features of asthma inhaler regimens.

In the survey you'll be shown between 10 and 20 scenarios, it's different each time and for each person. In the scenarios you'll be asked to pick which of the two imaginary asthma inhaler regimens shown you'd prefer or that they are both the same.

As you go through the scenarios two features of asthma inhaler regimens will be shown and will be different between the two options. For the survey **you'll need to assume that everything else is the same apart** from the two varying features shown on the screen.

You might feel that the scenarios are very similar or the same as ones you've seen before. They will be subtly different and it's the programme trying to work out exactly what is most important to you.

Below are a couple pictures of what the survey will look like, based on some features of buying a house in Wellington.

Please ask if you've got any questions!

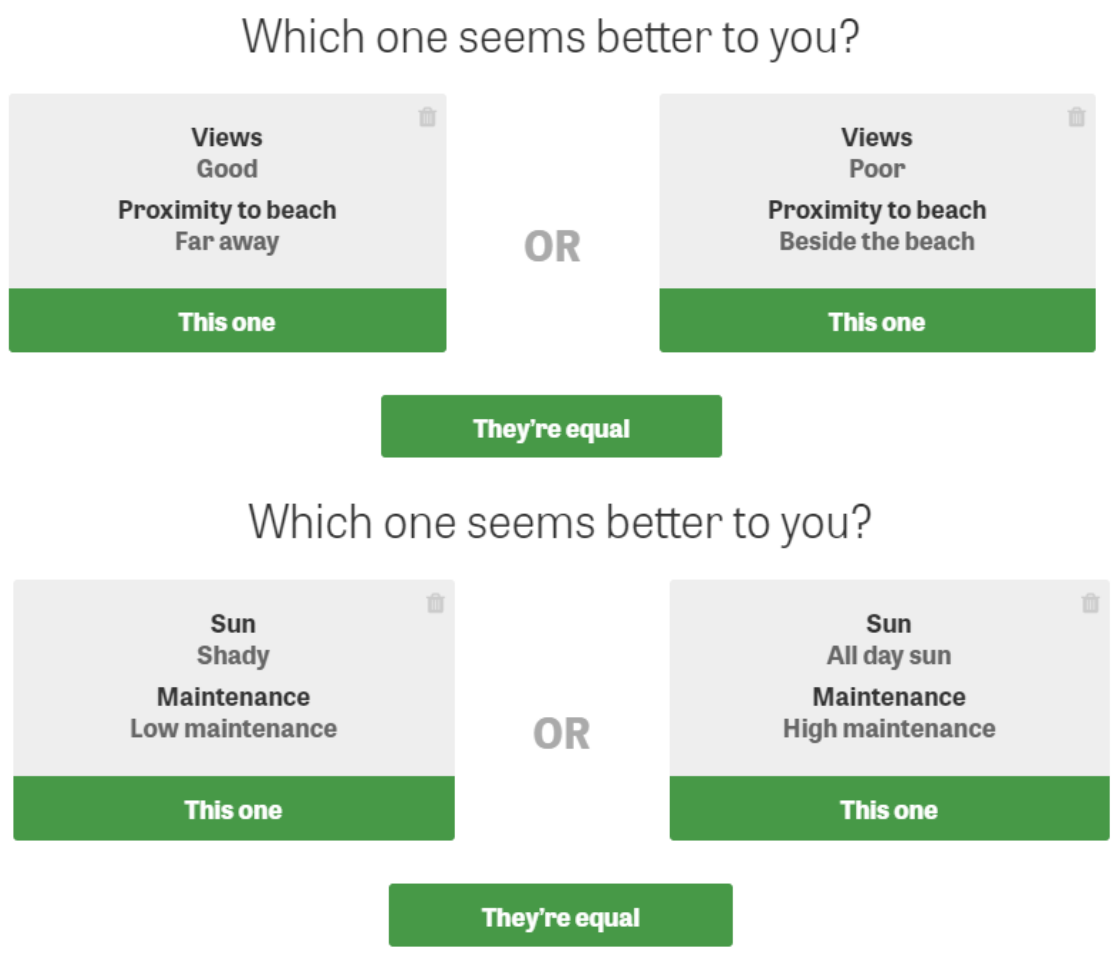

Figure 27: Participant explanation the rational for the DCE sheet

5.3.7. Data analysis

The 1000minds software uses linear-programming methods to derive weights for each attribute overall and also for the levels on each attribute, based on participant responses.[302] As well as each participant's weights, these individual outputs are averaged across all participants.

Continuous variables are described by mean (SD) or median (IQR). Categorical variables are described by counts and proportions as percentages.

5.4. Results

Participants

There were 407 participants eligible to complete the DCE. 296 (72%) started a DCE, one participant did not complete it. Seven participants answered both repeated questions inconsistently. These eight DCEs were excluded from the final analysis, therefore, 288 DCEs were included in the final data set. Overall, 185 participants (64%) expressed a preference for a "combined preventer and reliever inhaler taken as needed" so completed the as needed preference DCE, 103 participants (36%) expressed a preference for "a preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed" so completed the maintenance preference DCE. Characteristics of participants completing both DCEs are given in Table 34. Proportions of participants who had been randomised to each treatment arm differed between the two DCEs. This is because in the preferences survey 90% of those who had been randomised to as-needed budesonide-formoterol preferred as needed treatment and 10% preferred maintenance treatment. Of those randomised to maintenance budesonide 40% preferred as needed treatment and 60% preferred maintenance treatment. Otherwise participant characteristics were similar between the two DCEs.

Table 34: Characteristics of participants completing a DCE

Characteristic	As-needed preference DCE N=185	Maintenance preference DCE N=103
Randomised treatment		
Budesonide-formoterol no.(%)	125 (68)	14 (14)
Maintenance budesonide no.(%)	60 (32)	89 (86)
Baseline variables		
Age years	44.2 (15.3)	47.6 (17.8)
Age at diagnosis years	19.1 (18.4)	24.1 (20.9)
Female sex no.(%)	104 (56)	59 (57)
Ethnicity no.(%)		
Asian	8 (4)	8 (8)
NZ European	145 (78)	88 (85)
Māori	18 (10)	3 (3)
Other	3 (2)	2 (2)
Pacific	11 (6)	2 (2)
Smoking status no.(%)		
Current smokers	11 (6)	1 (1)
Ex-smokers	47 (25)	29 (28)
Never smokers	127 (69)	73 (71)
Pack years (among ever smokers)	5.5 (4.7) N=58	5.2 (5.4) N=30
ICS use at randomisation* no.(%)	122 (66)	79 (77)
Self-reported ICS adherence¥ – %	54.3 (36.7) N=122	61.7 (33.5) N=77
ICS use ever no.(%)	158 (85)	90 (87)
End-of-study variables		
Final visit ACQ-5†	0.82 (0.70)	0.64 (0.69)
Final visit on treatment FEV_1 % of predicted value	89.9 (15.0)	88.7 (15.6)
Final visit median FeNO ppb (IQR)	22 (15 to 38)	23 (15 to 40)
Participants experiencing ≥1 exacerbation or severe exacerbation during the study no.(%)	25 (14)	19 (10)
Early withdrawal no.(%)	8 (4)	11 (11)

Values are expressed as means (SD) or median (IQR) unless otherwise indicated

* Participants self-reported ICS use in the 12 weeks prior to randomisation

¥ Participant self-reported adherence to ICS in the 4 weeks prior to enrolment (% prescribed dose)

† The Asthma Control Questionnaire–5 (ACQ-5) consists of five questions that assess asthma symptoms in the previous week

The median number of choice profiles was 13 with a mean of 18.6 seconds per answer. Mean preference weights for the attributes and levels and attribute ranking for the two DCEs are reported in Table 35. In both DCEs, the attribute with the greatest preferences weight and the highest rank was 'shortness of breath in an average week' (with the most preferred level being 'not at all'). The preference weights and ranking of the other three attributes, 'treatment regimen', 'dose of

steroid' and 'likelihood of an asthma flare up', differed between the as-needed-preference and maintenance-preference DCEs. In the as-needed-preference DCE, 'likelihood of asthma flare up' was ranked second and 'treatment regimen' was ranked third, however they had similar mean preference weights, of 0.25 and 0.24 respectively; whereas the 'dose of steroid' attribute was the lowest ranked attribute with a preference weight of 0.17. In the maintenance-preference DCE, 'likelihood of asthma flare up' was the second highest ranked attribute and had a preference weight of 0.30. The attribute of 'dose of steroid' was ranked third and 'treatment regimen' was ranked fourth, however they had similar preference weights of 0.19 and 0.18 respectively. There was evidence of variability in preference for each attribute within both DCEs as indicated by the standard deviations. Mean preference weights within each DCE were similar irrespective of randomised treatment (Table 36).

Shortness of breath was the attribute which had the greatest influence on preference for asthma treatment out of the four included attributes in these DCEs conducted in participants with mild-moderate asthma completing the PRACTICAL study. Amount of shortness of breath had a similar preference weight in both DCEs indicating that it was of similar importance irrespective of participants' preferred treatment. The influence that the other three attributes exerted on preference varied depending on whether participants preferred a combined preventer and reliever inhaler taken as needed or a preventer inhaler taken twice a day with a reliever inhaler taken as needed.

Likelihood of an asthma flare up was ranked second in both the as-needed preference DCE and the maintenance preference DCE. However, in the as-needed preference DCE likelihood of an asthma flare up had a similar preference weight to treatment regimen (0.25 and 0.24 respectively). Indicating for those who prefer as-needed treatment their preferred regimen is of similar importance to them as risk of an asthma flare up. Dose of steroid was the lowest ranked attribute with a preference weight of 0.17 in the as-needed preference DCE indicating this attribute was the least important to participants. Within the maintenance preference DCE, risk of asthma flare up had a preference weight of 0.30, whereas treatment regimen had a preference weight of 0.18 and dose of steroid had a preference weight of 0.19. Whilst treatment regimen

was the least preferred attribute, it had a very similar preference weight to dose of steroid indicating that to patients who preferred maintenance treatment both of these attributes were of similar importance.

Table 35: Preference weights and overall attribute ranking

Attribute	Level	Mean preference weight	Attribute rank
As needed preference DCE, N=185			
Treatment regimen	A preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed	0 (0)	
	A combined preventer and reliever inhaler, taken as needed	**0.24** (0.11)	3
Dose of ICS	Medium	0	
	Low	0.10 (0.08)	
	Very low	**0.17** (0.11)	4
Risk of asthma flare up	20 out of 100 people in a year (20%)	0	
	10 out of 100 people in a year (10%)	0.14 (0.07)	
	5 out of 100 people in a year (5%)	**0.25** (0.09)	2
Shortness of breath in an average week	A moderate amount or more	0	
	A little	0.20 (0.09)	
	Not at all	**0.33** (0.12)	1
Maintenance preference DCE N=103			
Treatment regimen	A combined preventer and reliever inhaler, taken as needed	0 (0)	
	A preventer inhaler taken twice a day every day, with a reliever inhaler taken as needed	**0.18** (0.12)	4
Dose of ICS	Medium	0	
	Low	0.11 (0.08)	
	Very low	**0.19** (0.10)	3
Risk of asthma flare up	20 out of 100 people in a year (20%)	0	
	10 out of 100 people in a year (10%)	0.16 (0.08)	
	5 out of 100 people in a year (5%)	**0.30** (0.12)	2
Shortness of breath in an average week	A moderate amount or more	0	
	A little	0.19 (0.09)	
	Not at all	**0.34** (0.12)	1

Levels are presenting in order of increasing inherent ranking where the level with the lowest inherent ranking is given first and the level with the highest inherent ranking is given last in bold, and represents the preference weight for the attribute overall

Overall attribute preference weights (in bold) add to one

Table 36: Mean attribute preference weight by randomised treatment

Randomised treatment	Budesonide-formoterol as needed Mean preference weight	Maintenance budesonide Mean preference weight
As needed preference DCE N=185	N=125	N=60
Treatment regimen	0.25 (0.11)	0.22 (0.12)
Dose of ICS	0.18 (0.11)	0.17 (0.11)
Risk of asthma flare up	0.24 (0.09)	0.27 (0.09)
Shortness of breath in an average week	0.33 (0.12)	0.34 (0.12)
Maintenance preference DCE N=103	N=14	N=89
Treatment regimen	0.14 (0.11)	0.18 (0.13)
Dose of ICS	0.19 (0.09)	0.19 (0.11)
Risk of asthma flare up	0.34 (0.10)	0.29 (0.12)
Shortness of breath in an average week	0.33 (0.11)	0.34 (0.12)

5.5. Discussion

The finding that participants had the strongest preference for amount of shortness of breath is consistent with the previous DCEs reviewed in the Introduction which also found that shortness of breath or symptom frequency were important attributes that significantly affected preference[257,267,273–276]. Similar to other DCEs, asthma exacerbations or flare ups were also important to participants[273,276], however, the importance of asthma flare up varied depending on whether the participant preferred as-needed or maintenance treatment. Those who preferred as-needed treatment had an almost equal preference weight for risk of an asthma flare up and treatment regimen. Whereas those who preferred maintenance treatment had a higher preference weight for risk of asthma flare up which was similar to amount of shortness of breath. This indicates that for them breathlessness and risk of an asthma flare up were of similar importance. Previous DCEs have reported conflicting results regarding the importance of ICS dose to patients[267,269], however, in this study across both DCEs it was the least important attribute. No previous DCEs included an as-needed asthma regimen as an attribute, but previous studies found patients prefer regimens with fewer inhalers[257,269,273], or that are convenient to use and have a lower

dosing frequency[276]. Within this study the preference weight for treatment regimen in those who preferred as needed treatment was 0.24 versus 0.18 in those who preferred maintenance treatment indicating that participants had a greater strength of preference for as needed treatment compared to maintenance treatment.

Within each DCE, the mean attribute preference weights were similar irrespective of randomised treatment, suggesting that strength of preference for the attributes of a particular regimen was not determined by prior experience of that regimen during the RCT. This finding contrasts with the findings of the preference survey where preference for either as needed or maintenance treatment and preference for and beliefs about preventer inhaler use were strongly affected by randomised treatment.

Patient preferences for different attributes of asthma treatment can help determine which regimen is most suitable for them. The PRACTICAL study reported no difference between the treatment regimens in asthma symptoms as assessed by the group mean ACQ-5. However, the SYGMA[176,177] and Novel START[178] studies reported a slight increase in asthma symptoms with as-needed budesonide formoterol compared to maintenance budesonide. While either regimen may be suitable, if a patient has a strong preference to avoid symptoms then maintenance ICS may be more appropriate for them. The lower severe exacerbation rate with as-needed budesonide-formoterol compared to maintenance budesonide in the PRACTICAL and Novel START studies and similar rates between the two regimens in the SYGMA studies suggests as-needed budesonide-formoterol is more appropriate for patients in whom the priority is to avoid exacerbations. Exposure to ICS was significantly lower in the budesonide-formoterol group in all four studies therefore, budesonide-formoterol is a more appropriate regimen for patients who wish to limit their exposure to ICS. Understanding patients' preferences and priorities for asthma treatment is important when discussing management options with patients, particularly as as-needed budesonide-formoterol enters clinical practice.

5.5.1. Strengths and weaknesses

Weaknesses of DCE methodology were discussed in depth in the Introduction and apply to this DCE. In any DCE, hypothetical bias may have affected the results[262]. Attempts were made to mitigate this by only including attributes and levels that were realistic and relatable. Shortness of breath was the only symptom included in the DCE, whereas asthma also causes wheeze, cough and night waking, so the influence of other asthma symptoms on preference are unknown. Participants were aware of both treatments included, from personal experience in the case of their own randomised treatment, and for the other treatment, from information provided at randomisation and prior to completing the DCE. To limit cognitive burden and the number of questions in the DCE, we opted to include only four attributes which were considered to be important influencers of choice; but other attributes such as medication cost[267] may be relevant.

Other potential limitations are participants were asked to choose between hypothetical asthma treatments defined on just two attributes at a time. Therefore, they were not making each choice based on the full set of four attributes, and the results may be susceptible to bias as participants may have been making choices based on assumptions about the other two attributes[304,305]. However, the use of partial profiles can help mitigate effects of attribute dominance and reduces the complexity of choices for the participant[306]. The maintenance regimen offered in the DCE specified twice-daily treatment, as studied in PRACTICAL. However, there are ICS formulations approved for once-daily use, and specifying twice-daily treatment for the regimen attribute may have biased preferences towards the as-needed regimen.

Because the categorical attribute of regimen preference does not have an inherent ranking universally accepted by everyone, we developed two almost identical DCEs in order to utilise the PAPRIKA method. This study was conducted in participants completing an RCT, so the sample may not be representative of the general mild-moderate asthma population, who may have different preferences. A DCE was not

completed by 111 eligible participants (27%) and their preferences may be different from those who completed a DCE.

Strengths of this study are it is the first to investigate patient preferences for two specific asthma therapies using DCE methodology and demonstrates how investigation of patient preferences for attributes of asthma regimens can be incorporated into a RCT. Previous DCEs have explored patient preferences for attributes of asthma treatment,[269,271–273,276] but none has compared a regular versus an as-needed therapy and this is the first study to determine preferences for a current or desired asthma therapy. Because participants were asked to state their preference for one of the two regimens prior to commencing the DCE means that attribute preference weights are directly related to their preferred treatment regimen.

5.5.2. Future work

A DCE conducted in the general population which also includes other treatment regimens would help determine the strength of patient preferences for a wider range of different asthma treatment and attributes of these treatments. This would add to our understanding of patient preferences in the general population, which may be different to preferences of patients who are willing to participate in a clinical trial.

5.6. Conclusion

In conclusion, these results suggest that avoidance of shortness of breath was the most important aspect of asthma management to participants. However, the regimen patients preferred influenced whether they were willing to trade-off likelihood of an asthma flare up and steroid dose for their preferred treatment regimen. Participants who preferred symptom-driven treatment were willing to trade off on these two attributes whereas participants who preferred maintenance treatment were not. This indicates that participants who prefer symptom-driven treatment have a greater strength of preference for regimen than participants who prefer maintenance treatment. Knowledge of patient preferences for treatment attributes together with knowledge of regimen characteristics can be used in discussion with patients to

determine the most appropriate regimen for them, based on their preferences for regimen, shortness of breath, likelihood of an asthma flare up and steroid dose.

6. Conclusion

This thesis has investigated use of symptom-driven budesonide-formoterol in mild-moderate asthma, which is a novel regimen. Four different aspects of symptom-driven budesonide-formoterol have been explored; the efficacy and safety; exposure to ICS and beta$_2$-agonist and patterns of use; patient preference for symptom-driven treatment; and strength of patient preference for different aspects of asthma treatment. This provides data that has both breadth and depth on use of symptom-driven budesonide-formoterol in mild-moderate asthma.

The PRACTICAL study showed as-needed budesonide-formoterol lead to a 31% reduction in risk of a severe exacerbation compared to maintenance budesonide plus terbutaline as-needed, with no difference in asthma control (measured by ACQ-5) or FEV_1 between the two groups. While FeNO was higher in the as-needed budesonide-formoterol group the difference equated to 5ppb, which is of doubtful clinical significance. Effects of randomised treatment on severe exacerbation rate were similar across all subgroups. Therefore, clinical profiling of patients is not necessary because as-needed budesonide formoterol reduces exacerbation risk across all patient subgroups.

Following the publication of the SYGMA 1 and 2 studies[176,177], the 2019 update of the GINA strategy[288] replaced SABA reliever therapy with ICS-formoterol reliever therapy at Step 1 and suggested ICS-formoterol reliever therapy as an alternative to daily low dose ICS plus SABA reliever therapy at Step 2. The new treatment strategy is given in Figure 28. The new recommendations in the 2019 update were the most fundamental change in the GINA strategy for 30 years[307]. The findings from the PRACTICAL study[279] provide evidence which supports the inclusion of as-needed ICS-formoterol as an alternative to daily ICS at Step 2 in the GINA 2019 update and suggests that it may be the preferred option, particularly if decreased exacerbation risk is the clinical priority.

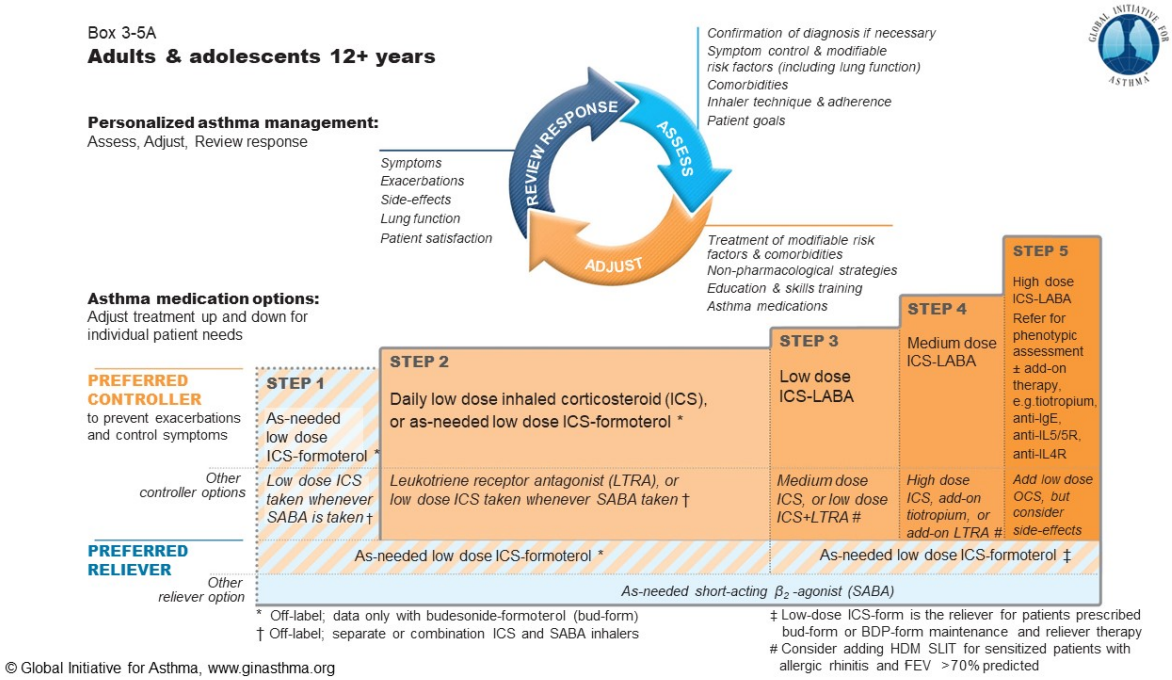

Figure 28: Global Initiative for Asthma 2019 stepwise approach to control asthma symptoms[288]
[Republished with permission © 2019, Global Initiative for Asthma, available from www.ginasthma.org, published in Fontana, WI, USA.]

In the PRACTICAL study, as-needed budesonide-formoterol lead to a decrease in risk of severe exacerbations and equivalent symptom control at 40% lower exposure to ICS. This was due to substantive periods of no use, coupled with more frequent periods of increased use suggesting that titrating budesonide-formoterol to symptoms and timing of medication use is more important than total dose of budesonide taken. This provides a mechanism for how a symptom-driven budesonide-formoterol achieves its clinical effects.

Patient preferences support use of as-needed budesonide formoterol because patients randomised to as-needed budesonide-formoterol were significantly more likely to prefer this regimen to maintenance treatment. They were satisfied with their study inhaler and confident in using budesonide-formoterol reliever therapy. The regimen that patients preferred was strongly associated with their randomised treatment, as was their response to questions on preference for and beliefs about preventer inhalers. This data indicates symptom-driven budesonide-formoterol aligns more closely with patients' preferences described in the literature for simple,

convenient treatment regimens that they are in control of and suggests that in clinical practice, a trial of as-needed treatment is likely to be appropriate to help patients decide which regimen they prefer.

The DCE found control of shortness of breath was the most important attribute of asthma treatment to all patients, however, patients who preferred as-needed treatment had a greater strength of preference for their preferred regimen. This supports the finding that 90% of patients randomised to as-needed budesonide-formoterol preferred as-needed treatment over maintenance treatment. This data has clinical applications because it can be used to guide discussions with patients regarding their priorities and preferences for attributes of asthma treatment which can be used in conjunction with data on regimen characteristics to determine the most appropriate regimen for them.

In conclusion, in this thesis I have demonstrated that symptom-driven budesonide-formoterol is an effective and safe novel treatment regimen in patients with mild-moderate asthma which is appropriate for most patients, will improve asthma outcomes and aligns with patient preferences for treatment.

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8. Appendix

8.1. Ethical approval for the PRACTICAL study

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Ministry of Health
Freyberg Building
20 Aitken Street
PO Box 5013
Wellington
6011

0800 4 ETHICS
hdecs@moh.govt.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 Long-Acting 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

8.2. Participant information and consent sheet for the PRACTICAL study

Participant information and consent 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:	

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.		

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.

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).

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:

Phone:

Email:

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 Sheet

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:

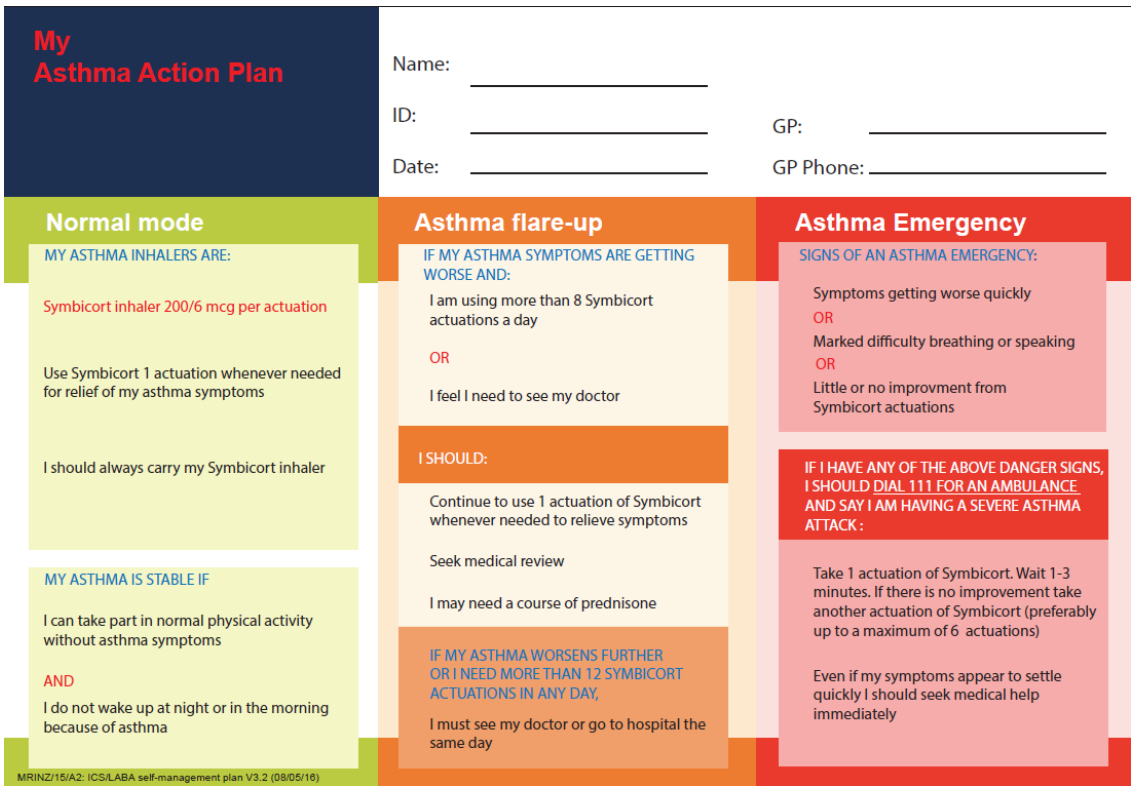
I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

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

Researcher's name:

Signature: Date:

8.3. Participant asthma action plans



My Asthma Action Plan

Name: _____

ID: _____ GP: _____

Date: _____ 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

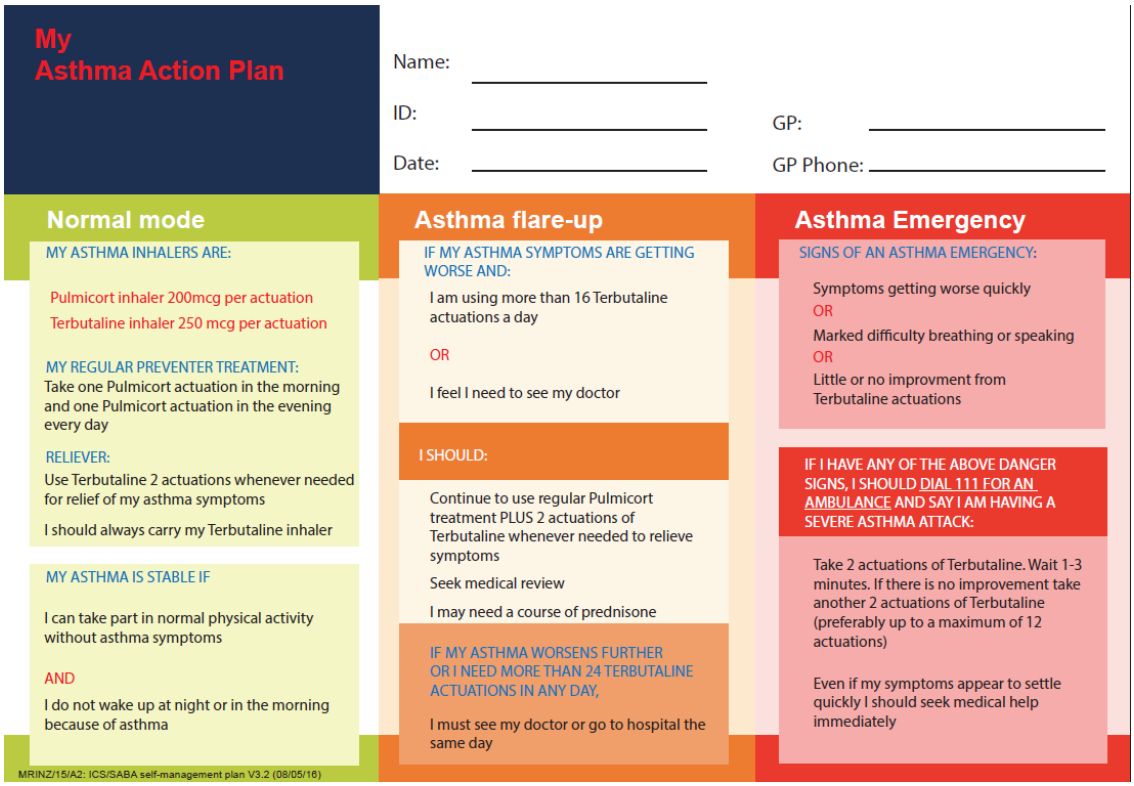
Little or no improvment from Symbicort actuations

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)



My Asthma Action Plan

Name: _____

ID: _____ GP: _____

Date: _____ 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 improvment 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)

8.4. Procedures for checking the electronic inhaler monitors

Initial Site Check

Open Smartinhaler Connection Centre. Connect device to the computer via a micro-USB cable.

Correct ID displayed by Smartinhaler Connection Centre? Yes ☐ No ☐

Click 'Start Download'. The pop-up window should say 'Total number of X logs have been uploaded to https://smartinhalerlive.com'. Please disregard the number of logs.

Successful log upload? Yes ☐ No ☐ If no, why not? _____

Unplug device from micro-USB cable.

Battery check green? Yes ☐ No ☐ if no, what colour? _____

Time colour co-ordinated test inhaler inserted into the device (hh:mm, 24h clock): _____

Screw inhaler cap on tightly (to allow foam to expand)

Assign device to the appropriate test patient profile on SmartinhalerLive website.

Wait 10 minutes (see manual for explanation)

Second log up load. Time_____

Has inhaler installed been registered Yes ☐ No ☐ If not then failed device.

Unplug USB cable.

First two actuations: put cap back on after 2 actuations.

First puff (hh:mm)	Wait 10-20 seconds	Second puff (hh:mm)	**Date & Signature:**
_ _ : _ _		_ _ : _ _	

Wait at least 15 minutes

Second two actuations: put cap back on after 2 actuations.

Third puff (hh:mm) _ _ : _ _	Wait 10-20 seconds	Fourth puff (hh:mm) _ _ : _ _	**Date & Signature:**

Time test inhaler removed from device (hh:mm, 24h clock):_____

Connect device to the computer via the micro-USB cable. Click 'Start Download'. The pop-up window should say 'Total number of X logs have been uploaded to https://smartinhalerlive.com' Please disregard the number of logs – this does not correspond to the number of actuations.

On the SmartinhalerLive website, select 'Medication use by device' in the results menu. In the drop down menu, select the ID for the device in question. Click 'Refresh' to view the actuations recorded by this device.

Review of data - any spurious or missed actuations?

☐ No ☐ Yes

If yes, the inhaler has failed testing. Provide detail below:

Date & Signature:

Pre dispensing and re-dispensing checks

Inhaler Brand	Monitor ID	Date today (dd/mmm/	Battery check green?	Time of first USB upload (hh:mm) 24h	Time inhaler inserted (hh:mm) 24h	Time of 2 test actuations (hh:mm) 24h	Time of second USB upload	2 test actuations correctly	Monitor Pass/Fail	Inhaler ID / Batch No.	Drug Expiry
			Yes ☐ No ☐			1. 2.		Yes ☐ No ☐	Pass ☐ Fail ☐	ID: Batch:	
			Yes ☐ No ☐			1. 2.		Yes ☐ No ☐	Pass ☐ Fail ☐	ID: Batch:	
			Yes ☐ No ☐			1. 2.		Yes ☐ No ☐	Pass ☐ Fail ☐	ID: Batch:	
			Yes ☐ No ☐			1. 2.		Yes ☐ No ☐	Pass ☐ Fail ☐	ID: Batch:	
			Yes ☐ No ☐			1. 2.		Yes ☐ No ☐	Pass ☐ Fail ☐	ID: Batch:	
			Yes ☐ No ☐			1. 2.		Yes ☐ No ☐	Pass ☐ Fail ☐	ID: Batch:	
			Yes ☐ No ☐			1. 2.		Yes ☐ No ☐	Pass ☐ Fail ☐	ID: Batch:	

Collection check

If there is visible damage or the battery check light does not flash green, proceed to upload data then follow instructions for failed monitors (see study manual)

Did the participant have any issues/problems with the inhalers or electronic monitors? Account for inhalers and monitors not brought into the unit and give details on usage.

Inhaler ID	Inhaler type	Expiry date	Monitor ID	Visible damage?	Battery check green?	Time of USB upload (hh:mm) 24h clock	Will monitor be redispensed?
				Yes ☐ No ☐	Yes ☐ No ☐		Yes ☐ No ☐
				Yes ☐ No ☐	Yes ☐ No ☐		Yes ☐ No ☐
				Yes ☐ No ☐	Yes ☐ No ☐		Yes ☐ No ☐
				Yes ☐ No ☐	Yes ☐ No ☐		Yes ☐ No ☐
				Yes ☐ No ☐	Yes ☐ No ☐		Yes ☐ No ☐
Collection check performed by:							
Signature:					Date (dd/mmm/yyyy):		

8.5. Outcomes of all dispensed electronic inhaler monitors

Outcome	**Number (%)**
Number of monitors dispensed over the course of the PRACTICAL study	816
Number of monitors lost	6 (0.7%)
Number of monitors returned	810 (99.3%)
Returned no faults	283 (35%)
Returned with low battery	480 (59%)
Failed re-dispensing checks	31 (4%)
Damaged	16 (2%)

8.6. Patient information and consent sheet for preferences survey and the discrete choice experiment

Participant Information and Consent Sheet

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

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:	

INTRODUCTION

Thank you for completing the PRACTICAL study. As part of the study you were randomised to either:

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)

Now that you have finished the study we would like to ask you some additional questions, to give us some more information to find out who would benefit the most from each regimen and how the different regimens affected peoples' asthma. This is optional and your decision whether or not to participate will not affect your health care in any way, or your future relationship with the MRINZ or your GP.

The questionnaires will take approximately 30 minutes to complete and are designed to find out which of the 2 asthma treatment regimens people prefer and how people used their inhalers during the study.

Ethical approval by the Northern B Health and Disability Ethics Committee has been granted for this extra element.

If you have any questions about the study please feel free to contact Christina Baggott:

Phone:

Email:

This document is 2 pages long, including the Consent Form. Please make sure you have read all the pages. If you require an interpreter, this will be arranged.

Privacy and Confidentiality

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

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

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.

Declaration by participant:

I hereby consent to answer the extra questions on my views about asthma and taking asthma medications.	Yes ☐	No ☐

Participant's name:

Signature: Date:

Declaration by member of research team:

I have given a verbal explanation of the additional elements outlined in this form to the participant, and have answered the participant's questions about them.

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

Researcher's name:

Signature: Date: