EFFICACY AND SAFETY OF MAINTENANCE AND RELIEVER COMBINATION BUDESONIDE/FORMOTEROL THERAPY IN ASTHMA PATIENTS AT RISK OF SEVERE EXACERBATIONS: A RANDOMISED CONTROLLED TRIAL

MITESH DILIPKUMAR KANTILAL PATEL

BMedSci, BMBS, MRCP (UK)

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Abstract

The Single combination budesonide/formoterol inhaler as Maintenance And Reliever Therapy (SMART) regimen reduces severe asthma exacerbations, but it is uncertain whether it increases the risk of adverse effects due to high corticosteroid and beta-agonist doses with both short-term and cumulative exposure in patients at risk of severe exacerbations. The primary hypothesis was that the SMART regimen would reduce the risk of beta-agonist overuse. Secondary aims were to investigate whether patients treated with the SMART regimen were less likely to seek medical review in the setting of beta-agonist overuse and to determine whether any reduction in severe asthma exacerbations would be at a cost of a higher systemic corticosteroid burden.

This 24-week, open-label, parallel-group, multicentre randomised controlled trial randomised 303 asthma patients with a recent exacerbation to combination 200/6µg budesonide/formoterol metered dose inhaler (MDI) according to the SMART regimen (two actuations twice daily as maintenance with one extra actuation as-needed for relief of symptoms) or a fixed-dose regimen (two actuations twice daily as maintenance) with one to two actuations of 100µg salbutamol MDI as-needed for relief of symptoms (the 'Standard' regimen), with electronic monitoring to measure actual medication use. The use of electronic monitoring allowed beta-agonist overuse to be applied as a marker of the risk of life-threatening asthma. The primary outcome was the proportion of participants with at least one high beta-agonist use episode (more than eight actuations per day of budesonide/formoterol in addition to

the four maintenance doses in the SMART group or more than 16 actuations per day of salbutamol in the Standard group).

There was no significant difference between groups in the proportion of participants with at least one high use episode: SMART 84/151 (55.6%) versus Standard 68/152 (44.7%), relative risk (95% CI) 1.24 (0.99 to 1.56), p=0.058. There were fewer days of high use in the SMART group [mean (SD) 5.1 days (14.3) versus 8.9 days (20.9), relative rate (95% CI) 0.58 (0.39 to 0.88), p=0.01]. Of the participants who had at least one high use episode, those in the SMART group had fewer days of high use without medical review [mean (SD) 8.5 days (17.8) versus 18.3 days (24.8), relative rate (95% CI) 0.49 (0.31 to 0.75), p=0.001]. The SMART regimen resulted in higher inhaled corticosteroid exposure [mean (SD) 943.5µg budesonide per day (1502.5) versus 684.3µg budesonide per day (390.5), ratio of means (95% CI) 1.22 (1.06 to 1.41), p=0.006], but reduced oral corticosteroid exposure [mean (SD) 77.5mg prednisone (240.5) versus 126.6mg prednisone (382.1), p=0.011], with no significant difference in composite systemic corticosteroid exposure [mean (SD) 793.7mg prednisone equivalent per year (893.1) versus 772.1mg prednisone equivalent per year (1062.7), ratio of means (95% CI) 1.03 (0.86 to 1.22), p=0.76]. Participants in the SMART group had fewer severe asthma exacerbations [35 (weighted mean rate per year 0.53) versus 66 (0.97), relative rate (95% CI) 0.54 (0.36 to 0.82), p=0.004].

The SMART regimen has a favourable risk/benefit profile in patients at risk of severe asthma exacerbations.

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List of Symbols, Abbreviations and Nomenclature

Abbreviation/Symbol	Definition
ACTH	Adrenocorticotropic hormone
ACQ	Asthma Control Questionnaire
ADRB2	Beta-2 Adrenoceptor
AE	Adverse Event
AF	Atrial Fibrillation
AMD	Adjustable Maintenance Dosing
cAMP	Cyclic Adenosine Monophosphate
ANZCTR	Australian New Zealand Clinical Trials Registry
ATS	American Thoracic Society
BP	Blood Pressure
BTS	British Thoracic Society
CBP	Conventional Best Practice
CCDHB	Capital & Coast District Health Board
CD	Compact Disc
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airways Pressure
DPI	Dry Powder Inhaler
ED	Emergency Department
ERS	European Respiratory Society
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
HFA	Heptafluoropropane
HPA axis	Hypothalamic-Pituitary-Adrenal axis
ICC	Intra-class Coefficient

ICS	Inhaled Corticosteroid
ID	Identification
IV	Intravenous
LABA	Long-Acting Beta-Agonist
µg	Micrograms
MDI	Metered Dose Inhaler
Medsafe	New Zealand Medicines and Medical Devices Safety Authority
MRINZ	Medical Research Institute of New Zealand
MSA	Multiple Simultaneous Actuations
NIV	Non Invasive Ventilation
NZ	New Zealand
OR	Odds Ratio
PC	Personal Computer
PC_{20}	Provocative Concentration $_{20}$
PEFR	Peak Expiratory Flow Rate
RCT	Randomised Controlled Trial
RR	Relative Risk
SABA	Short-Acting Beta-Agonist
SAE	Serious Adverse Event
SATQ	Satisfaction with Asthma Treatment Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SMART	Single combination inhaler as Maintenance And Reliever Therapy

Chapter One: Introduction

1.1 Thesis aim

In asthma patients who are not controlled on inhaled corticosteroid (ICS) therapy, the standard treatment is a single combination ICS and long-acting beta-agonist (LABA) inhaler for fixed-dose maintenance therapy with a short-acting beta-agonist (SABA), such as salbutamol, for relief of symptoms.

An alternative approach is the Single combination inhaler as Maintenance And Reliever Therapy (SMART) regimen, in which patients use a combination budesonide/formoterol ICS/LABA inhaler as regular maintenance therapy and take extra doses of the same inhaler for relief of symptoms. This method of using a single budesonide/formoterol inhaler for both maintenance and relief is possible because formoterol is a beta-2 agonist with high intrinsic activity which has an onset of action comparable to salbutamol and a duration of action for over 12 hours. Formoterol, in combination with budesonide, can therefore provide sustained bronchodilation when used as maintenance treatment and may also be used as a reliever treatment.

Prior randomised controlled trials (RCT) have demonstrated that in patients with poorly controlled asthma, treatment with the SMART regimen reduces severe asthma exacerbations when compared to the 'Standard' regimen of the same fixed-dose maintenance budesonide/formoterol with SABA for relief. The generalisability of

this finding is limited for three reasons. Firstly, these trials excluded potentially eligible patients with high baseline reliever medication use. Secondly, a reduction in maintenance ICS dose occurred at randomisation, in patients with current asthma symptoms. Thirdly, patients were required to demonstrate significant bronchodilator reversibility in order to be eligible.

In addition, these studies used daily diaries to collect data on use of inhaled medication, which is recognised to be an inaccurate measure of actual use of inhaled therapy when compared to electronic monitoring. As a result, it is not possible to determine if the reduction in severe exacerbations observed with the SMART regimen is due to a reduction in non-adherence to regular budesonide/formoterol therapy, or due to self-titrated increasing budesonide/formoterol use during worsening asthma. It is also unknown if the SMART regimen may lead to a greater delay in seeking medical care in the setting of beta-agonist overuse or whether it results in a greater systemic corticosteroid burden.

The principal study that this thesis describes is a 24-week, multicentre, open-label, randomised, parallel-group trial to study the efficacy and safety of the SMART regimen compared to Standard therapy in 303 real-world asthma patients who were at risk of severe exacerbations. The trial was designed to overcome the key limiting issues described above and used electronic monitoring to measure actual patterns of inhaler use.

Three supporting studies are also described. The first study investigated the accuracy of self-report compared to electronic monitoring of inhaled asthma medication use,

using data from a previously undertaken RCT of adherence to maintenance ICS and LABA treatments. The second study was a six-month bench validation of the accuracy of the electronic monitors that were used in the principal trial. The third study reports on the performance of the electronic monitors used in the principal trial, based on the use of pre-trial and within-trial validation protocols.

1.2 Thesis outline

Chapter One begins with a summary of the pharmacology and efficacy of ICS and a review of the comparative pharmacology of beta-agonists. The first half of this chapter then focuses on the evidence for the efficacy of formoterol in adult asthma and the current evidence for the SMART regimen is critically appraised. The second part of Chapter One focuses on the issues regarding the safety of beta-agonist drugs in asthma and in particular, the potential mechanisms of adverse effects with the use of formoterol. The methods used to measure adherence to inhaled treatment are also reviewed. The chapter ends with the hypothesis for the study and a summary of the aims for this thesis.

Chapter Two describes the design and findings of the first supporting study, investigating the accuracy of self-report compared to electronic monitoring as measures of use of inhaled asthma treatment. This study was a retrospective analysis of a recently conducted RCT by the Medical Research Institute of New Zealand

(MRINZ) research group, in which adherence to single and combination maintenance ICS and LABA therapy was measured using electronic monitoring.

Chapter Three reports on the design and results of the six-month bench testing of the Smartinhaler Tracker electronic monitors. This chapter is a validation of the methods used for the principal RCT, and the findings were used to inform the study protocols for the use of the electronic monitors in the principal study.

Chapter Four describes the design and methods for the randomised controlled trial investigating the efficacy and safety of the SMART regimen in adult asthma patients at risk of severe exacerbations (referred to as 'the SMART study' in this thesis).

Chapter Five details the pre-trial and within-trial quality control protocols for the use of the electronic monitors in the SMART study. This Chapter also describes the development and use of the computer software and website database used to manage data recorded by the electronic monitors.

Chapter Six presents the results of the SMART study. This chapter also details the performance of the electronic monitors in the trial.

Chapter Seven is a discussion of the findings, including the strengths of the study, placing the study in context with prior research, and methodological limitations. The Chapter ends with the overall conclusions from the SMART study.

1.3 Inhaled budesonide

1.3.1 Pharmacology

Inhaled budesonide is a corticosteroid with topical anti-inflammatory action, which binds to glucocorticoid receptors present in airway cells and subsequently exerts its anti-inflammatory action by altering gene transcription (Chung, Caramori and Adcock, 2009; Lindmark, 2008). Budesonide acts by reducing airway inflammatory cells and the release of inflammatory mediators (Brogden and McTavish, 1992; Laitinen, Laitinen and Haahtela, 1992).

1.3.2 Therapeutic efficacy

Treatment with inhaled budesonide improves airway hyper-responsiveness, asthma symptoms and lung function and reduces severe exacerbations of asthma (Pauwels et al., 2003a; Wongtim et al., 1995; Haahtela et al., 1991; Juniper et al., 1990). Regular use of ICS therapy also reduces the risk of death from asthma (Suissa et al., 2000).

There is evidence for a dose-response therapeutic effect for budesonide (Masoli et al., 2004), though most of the clinical benefits are derived at low to medium daily maintenance doses (up to 800µg per day) (Adams and Jones, 2006). Patients with more severe asthma may benefit from higher daily doses or increased frequency of dosing (Adams and Jones, 2006; Toogood et al., 1982).

1.3.3 Systemic absorption

Lung absorption and gastro-intestinal absorption of ICS both contribute to systemic availability (Barnes, 1998). Following systemic absorption, budesonide undergoes extensive first-pass hepatic metabolism into low-activity metabolites (Lee and Corren, 2008; Brogden and McTavish, 1992). Plasma half-life is relatively short at two to three hours (Brogden and McTavish, 1992).

1.3.4 Adverse effects

The most common local side effects are dysphonia, oropharyngeal candidiasis, sore throat and cough (Brogden and McTavish, 1992).

Systemic adverse effects are determined by the amount of drug that is systemically bioavailable and include suppression of the hypothalamic-pituitary-adrenal (HPA) axis, inhibition of bone metabolism and cataract formation (Barnes, 1995b). These effects are unlikely to occur at the usual prescribed maintenance doses of budesonide, but patients may be at greater risk of these adverse effects after high-dose, prolonged exposure (Dluhy, 1998; Pedersen and O'Byrne, 1997; Barnes and Pedersen, 1993). The risk of both short-term and long-term ICS-related adverse events may therefore be greater with the SMART regimen in comparison to a fixed-dose regimen with SABA for relief.

1.3.5 Bioequivalent doses of inhaled budesonide and oral prednisone for systemic effect on HPA axis function

Stimulation tests are considered sensitive methods for assessing the effects of ICS on HPA axis function (Barnes, Pedersen and Busse, 1998; Pedersen and O'Byrne, 1997).

A dose-response study compared the effect of budesonide (via Turbohaler) and 10mg of prednisone over six weeks in asthma patients, using adrenocorticotropic hormone (ACTH) infusion to assess HPA axis function (Aaronson et al., 1998). The investigators calculated that 10mg oral prednisone was bioequivalent to 5mg of inhaled budesonide, for systemic effect on adrenal function.

1.4 Beta-2 adrenoceptor structure and function

Beta-2 adrenoceptors are transmembrane proteins which, when activated by agonist drugs, stimulate the production of the second messenger cyclic adenosine monophosphate (cAMP) via G-proteins (Anderson, 2000; Barnes, 1995a). Increased cAMP concentration, through a series of intracellular reactions, leads to smooth muscle relaxation and bronchodilation (Anderson, 2000; Barnes, 1995a).

1.5 Pharmacological properties of beta-2 agonists

In order to understand the relative clinical efficacy and adverse effect profile of beta-2 agonists, several important pharmacological properties need to be considered.

1.5.1 Intrinsic activity

Intrinsic activity refers to 'the ability of a drug to activate its receptor independent of its concentration' (Cates, Lasserson and Jaeschke, 2009; Hanania et al., 2002). Beta-agonists which completely activate the beta-2 adrenoceptor are called full agonists (e.g. isoprenaline and adrenaline), whilst those that partially activate the receptor are called partial agonists (e.g. formoterol, salbutamol and salmeterol) (Hanania et al., 2002). Partial agonists are further classified as 'strong partial agonists' (e.g. formoterol) and 'weak partial agonists' (e.g. salmeterol) on the basis of their intrinsic activity (Hanania et al., 2002). Drugs with higher intrinsic activity have the capacity for greater receptor activation and therefore greater maximal effect (Hanania et al., 2002).

Beta-agonists with high and low intrinsic activities may be capable of eliciting different clinical responses during stable and unstable asthma (Hanania et al., 2002). For instance, during stable asthma where beta-adrenoceptor function may be unimpaired, agonists with high and low intrinsic activity may provide similar levels of bronchodilation and bronchoprotection (Hanania et al., 2002; Rabe et al., 1993). On the other hand, during acute asthma or in patients with more severe disease, impairment of beta-2 adrenoceptor function may occur (e.g. due to uncoupling of the

receptor and G-protein), together with airway smooth muscle contraction (Anderson, 2000; Barnes, 1995a). In this situation, agonists with higher intrinsic activity may elicit greater bronchodilation compared to those with lower intrinsic activity, and may also provide greater protection against bronchoconstrictive stimuli (Palmqvist et al., 1999; Molimard et al., 1998).

However, in the setting of worsening asthma where high doses of beta-agonists may be used for relief of symptoms, agonists with higher intrinsic activity may also cause a greater degree of extra-pulmonary beta-2 adrenoceptor-mediated adverse effects, such as hypokalaemia (Hanania et al., 2002; Palmqvist et al., 1999; Newhouse et al., 1996).

Furthermore, inhaled beta-2 agonists may also have intrinsic activity for activation of the beta-1 adrenoceptor, resulting in the cardiac adverse effects associated with chronotropy and inotropy (Bremner et al., 1996; Newhouse et al., 1996). Thus, a situation arises whereby a beta-2 agonist may allow greater therapeutic effect due to its high intrinsic activity at the beta-2 adrenoceptor in the lung, but may also increase the risk of adverse effects due to high intrinsic activity at extra-pulmonary beta-2 or beta-1 adrenoceptors.

Intrinsic activity is therefore an important determinant of the risk/benefit profile of beta-agonist medication, particularly in the setting of acute asthma and high reliever medication use.

1.5.2 Selectivity

Selectivity refers to the 'ability of a drug to bind to one receptor over another' (Cates et al., 2009). In the context of beta-agonists, selectivity may help to determine the balance between a therapeutic effect (e.g. beta-2 adrenoceptor mediated bronchodilation) versus an adverse effect (beta-1 adrenoceptor mediated tachycardia). This risk/benefit profile may be more complicated, as some extra-pulmonary adverse effects may also be beta-2 adrenoceptor mediated (e.g. hypokalaemia) (Newnham et al., 1995), whilst cardiac responses may also be associated with beta-2 receptor stimulation in the heart (Brodde and Michel, 1999; Anderson, 1993).

1.5.3 Tachyphylaxis/Tolerance

Tachyphylaxis is defined as 'the reduced responsiveness of a tissue to an agonist on continued or repeated exposure to an agonist' (Hanania et al., 2002). Tolerance is often used synonymously with tachyphylaxis, though tolerance may be considered to develop over a longer time period than tachyphylaxis (Rang, 2003).

Tolerance to both the pulmonary and systemic effects of beta-agonists may occur, and drugs with higher intrinsic activity may produce greater tolerance than those with lower intrinsic activity (Hanania et al., 2002). This may occur via a number of mechanisms, including down-regulation of receptor function or a change in receptor activation of second messenger systems (Rang, 2003).

1.5.4 Comparative pharmacology of beta-agonists

The key comparative pharmacological properties are summarised in Table 1.1 (Baker, 2010; Hanania et al., 2002; Naline et al., 1994; Decker et al., 1982; O'Donnell, 1972).

Formoterol has greater intrinsic activity than salbutamol, and is also more beta-2 selective. Thus, it may produce greater maximal therapeutic effect in the setting of beta-agonist overuse.

These pharmacological properties will be further discussed when the safety of beta-agonists are reviewed later.

Table 1.1: Comparative pharmacology of beta-2 adrenoceptor agonists - efficacy

Beta-agonist	Intrinsic activity at the beta-2 adrenoceptor * (%)	Selectivity †	*In vitro* onset of action (min) ‡	*In vitro* duration of action (min) §
Isoprenaline	100.0	0.9	0.65	4.22
Fenoterol ‖	42.0	26	3.52	7.21
Formoterol	20.0	204	2.14	33.9
Salbutamol ‖	4.9	42	1.90	7.59
Salmeterol	<2.0	-	6.40	102.2

*: Higher values are interpreted as greater ability for receptor activation and maximal effect. †: Relative potency in trachea compared to atria of guinea-pig [this is a measure of the ratio of pulmonary to cardiac adrenoceptor action; higher values suggests greater relative beta-2 selectivity]. Comparative values for salmeterol from similar experiments in human tissue suggest that it has greater selectivity than formoterol. ‡: Time to attainment of 50% maximal relaxation in human bronchus. §: Time from washing the preparation to attainment of 50% recovery of basal tone in human bronchus. ‖: Selectivity data from O'Donnell (1972).

[Summarised and adapted from Baker (2010); Hanania et al. (2002); Naline et al. (1994); Decker et al. (1982); O'Donnell (1972)].

1.6 Inhaled salbutamol

1.6.1 Pharmacology

Salbutamol is a short-acting, selective, partial beta-2 agonist with a dose-response bronchodilatory effect (Price and Clissold, 1989). Maximal bronchodilation occurs within 15 to 30 minutes, and the duration of effect is approximately four to six hours (Price and Clissold, 1989). After systemic absorption, salbutamol is metabolised into inactive compounds in the liver, with an elimination half-life of approximately four hours (Price and Clissold, 1989).

1.6.2 Therapeutic efficacy

Salbutamol is the established treatment for relief of bronchoconstriction during worsening asthma and acute severe asthma (Lemanske and Busse, 2003).

1.6.3 Adverse effects

Short-term adverse effects include tachycardia, palpitations, tremor and muscle cramps (GlaxoSmithKline Limited, 2011; Price and Clissold, 1989). These effects are generally self-limiting.

A prior study suggested that regular treatment with salbutamol may produce tolerance to its bronchoprotective effects (Cockcroft et al., 1993). However, subsequent clinical trials did not demonstrate a worsening in clinical control with

regular salbutamol compared to as-required use (Dennis et al., 2000; Drazen et al., 1996; Chapman, Kesten and Szalai, 1994). Current asthma guidelines recommend that salbutamol is used 'as-required' for the relief of asthma symptoms and that increasing use is a marker of poor asthma control (SIGN/BTS, 2012; GINA, 2011).

1.7 Pharmacology of inhaled formoterol

Formoterol is a long-acting, selective, beta-2 adrenoceptor agonist with high intrinsic activity (Faulds, Hollingshead and Goa, 1991). It produces dose-dependent bronchodilation, with a rapid onset of action of two to three minutes (Faulds et al., 1991). Maximum bronchodilation occurs after two to four hours, with effects persisting for at least 12 hours (Lindmark, 2008; Faulds et al., 1991). Elimination half-life is approximately two hours (Faulds et al., 1991).

1.8 Therapeutic efficacy of formoterol

The efficacy of formoterol has been studied after short-term dosing, twice-daily longer term dosing and with 'as-needed' reliever use. These will be considered in turn below.

1.8.1 Short-term dosing

Initial studies demonstrated a rapid increase in Forced Expiratory Volume in 1 second (FEV_1) and a fall in specific airways resistance following dosing with formoterol and established a dose-response effect on bronchodilation (Derom and Pauwels, 1992; Lofdahl and Svedmyr, 1989).

The maximal increase in FEV_1 over four hours is greater after dosing with 12 actuations (72µg) of formoterol compared with 18 actuations (1800µg) (Rosenborg et al., 2002) or 24 actuations (2400µg) (Boonsawat et al., 2003) of salbutamol.

1.8.2 Speed of onset

Formoterol has a rapid onset of action, with up to 90% of its maximal bronchodilation occurring within the first 10 minutes after inhalation (Tattersfield, 1993; Derom and Pauwels, 1992; Becker and Simons, 1989). When compared to 100µg and 200µg of salbutamol, dosing with formoterol 6µg and 12µg respectively results in comparable increases in FEV_1 at three minutes (Seberova and Andersson, 2000). Formoterol reverses bronchoconstriction induced by methacholine within eight minutes, which is comparable to the effect of salbutamol (Politiek, Boorsma and Aalbers, 1999) and provides symptomatic relief from dyspnoea within one minute after inhalation (van der Woude, 2002).

1.8.3 Duration of action

The duration of bronchodilation is greater after dosing with 12 to 24µg of formoterol compared to dosing with 200µg salbutamol, and lasts for at least 12 hours (Derom and Pauwels, 1992; Maesen et al., 1992; Sykes and Ayres, 1990).

Formoterol provides prolonged protection against methacholine-induced bronchoconstriction for between 12 to 24 hours (Rabe et al., 1993; Ramsdale et al., 1991). Peak bronchodilation occurs between three and five hours (Rosenborg et al., 2002; Ringdal et al., 1998; Palmqvist et al., 1997; Sykes and Ayres, 1990).

1.8.4 Protection against bronchoconstrictor stimuli

Formoterol protects against the bronchoconstriction stimulus produced by histamine (Sovijarvi et al., 1992), adenosine 5'-monophosphate (AMP) (Ketchell et al., 2002; Nightingale, Rogers and Barnes, 1999), exercise (McAlpine and Thomson, 1990) and hyperventilation (Malo et al., 1990). The protection against the late asthmatic reaction to inhaled allergen is greater with formoterol than with salbutamol (Palmqvist et al., 1992).

1.8.5 Longer-term dosing

Regular formoterol provides significantly greater protection against methacholine-induced bronchoconstriction than on-demand salbutamol over a 24-week period and was significantly superior with regards FEV_1, peak expiratory flow rate (PEFR), symptom scores and rescue medication use (FitzGerald et al., 1999).

Regular formoterol improves symptoms, lung function and rescue medication use when compared with placebo, regular terbutaline or regular salbutamol (Ekstrom et al., 1998; Schreurs et al., 1996; Steffensen et al., 1995; Kesten et al., 1991).

1.8.6 Addition of formoterol to inhaled corticosteroids for maintenance therapy

A series of studies demonstrated the efficacy of formoterol when added to ICS therapy (Gibson, Powell and Ducharme, 2007). Firstly, the addition of formoterol to ICS significantly improved asthma symptoms and lung function compared to the addition of placebo to ICS (van der Molen et al., 1997).

The Formoterol And Corticosteroid Establishing Therapy (FACET) investigators (Pauwels et al., 1997) demonstrated the efficacy of formoterol as an add-on maintenance therapy in patients with stable asthma. In this trial, the effects of adding formoterol (12µg twice daily) to both lower (100µg twice daily) and higher (400µg twice daily) doses of budesonide were studied. The addition of formoterol to either low- or high-dose budesonide significantly reduced severe exacerbations compared to low- or high-dose budesonide alone respectively. Low-dose budesonide and formoterol in combination was also superior to higher dose budesonide in improving asthma symptoms.

There were other important findings from this study. Increasing the budesonide dose four-fold had a significantly greater impact on reducing asthma exacerbations than the addition of formoterol to low-dose budesonide, suggesting that high doses of inhaled corticosteroids may have greater efficacy in the reduction of severe exacerbations.

Of the patients in the two formoterol-treated groups, those treated with high-dose budesonide plus formoterol (receiving 400µg budesonide/12µg formoterol twice daily) experienced significantly fewer severe exacerbations than patients in the lower dose budesonide plus formoterol group (receiving 100µg budesonide/12µg formoterol twice daily), supporting the use of the higher-dose combination treatment in patients with greater asthma severity.

The subsequent analysis by Tattersfield et al. (1999) described the change in symptoms, PEFR and reliever medication use around the time of severe asthma exacerbations. This graphical description of the time course of severe exacerbations (Tattersfield et al., 1999) is important when considering the potential mechanisms of the efficacy benefits seen with the SMART regimen, and is discussed further later.

Finally, the results from Group B in the OPTIMA study provided evidence for the benefits of formoterol in addition to ICS in patients with mild but symptomatic asthma (O'Byrne et al., 2001). Addition of formoterol to ICS reduced asthma exacerbations and improved asthma control and lung function to a greater extent than doubling the dose of ICS.

1.8.7 As-needed formoterol use as a reliever

Short-term studies demonstrated that formoterol had comparable efficacy to salbutamol when used as a reliever treatment in stable (Wallin et al., 1990) and acute asthma (Boonsawat et al., 2003).

A large-scale double-blind RCT investigated the use of formoterol as a reliever compared to terbutaline (Tattersfield et al., 2001). This trial, extending the findings of the FACET study, compared 6µg of formoterol and 500µg of terbutaline when used for relief of symptoms in patients on ICS who were symptomatic during run-in. The most symptomatic patients (those using greater than 12 inhalations per day of rescue medication during run-in) were excluded from study entry.

The time to first exacerbation was significantly prolonged in the formoterol group, and there was a significant 45% reduction in severe asthma exacerbations. Patients in the formoterol group had a significant reduction in reliever use during the study period and significant increases in PEFR and pre-bronchodilator FEV_1. Study withdrawals and the occurrence and patterns of adverse events (AE) and serious adverse events (SAE) were similar between the groups. Both groups used on average 1.32 inhalations of study drug per occasion to relieve symptoms, suggesting that patients in both groups perceived similar levels of symptomatic improvement with their reliever therapy.

Two important issues require consideration regarding this study. Firstly, patients who used greater than 12 inhalations per day or those who had a second severe exacerbation during the study were withdrawn, limiting the generalisability of the findings to asthma patients with high beta-agonist use, or patients who have more severe asthma. Secondly, patients in this study were not receiving maintenance LABA therapy.

This second issue was addressed by the subsequent RELIEF study (Pauwels et al., 2003b), in which the effects of formoterol as a reliever were investigated in asthma patients who were permitted maintenance LABA therapy.

The RELIEF investigators (Pauwels et al., 2003b) compared as-needed 6µg formoterol with 200µg salbutamol over a six-month study period in patients with asthma. 76% of patients were on maintenance ICS therapy and 31% on LABAs at study entry. The time to first asthma exacerbation was significantly prolonged in the formoterol group, with a significant 13% reduction in the risk of an exacerbation requiring oral corticosteroids. There were significantly fewer days with asthma symptoms in the formoterol group.

These studies established the efficacy of the symptom-driven use of formoterol as a reliever medication. This concept was developed in studies investigating the as-required, symptom-driven use of ICS and SABA therapy and ICS and LABA therapy in mild asthma.

1.9 Use of as-needed ICS+SABA therapy in mild asthma

Three trials, two in adults (Calhoun et al., 2012; Papi et al., 2007) and one in children (Martinez et al., 2011), have compared the efficacy of as-needed ICS+SABA therapy with regular ICS therapy (with SABA as-needed) in mild asthma. The adult trials will be discussed further.

The first trial was a study of mild adult asthma patients, two thirds of whom were not on regular ICS (Papi et al., 2007). Patients were well-controlled during run-in and randomised to as-needed combination ICS/SABA (beclomethasone/salbutamol), as-needed SABA (salbutamol), regular ICS (with salbutamol as-needed), or regular ICS/SABA (with salbutamol as-needed). Patients were not provided with written asthma self-management plans and were instructed to use their reliever treatments as guided by their symptoms.

The risk of an asthma exacerbation was not significantly different between the as-needed combination group and regular ICS group. Symptom-free days were not significantly different between the as-needed combination group and both the regular ICS and regular combination therapy groups. However, cumulative ICS dose was significantly lower in the as-needed combination group compared to both the regular therapy groups.

This study demonstrated that the symptom-driven use of combination ICS/SABA therapy was comparable to regular ICS therapy in providing protection against asthma exacerbations. This finding indicates that exposure to ICS at the time of worsening asthma may be a potential advantage of the as-needed combination therapy approach.

In a subsequent study of asthma patients who were controlled on low-dose ICS, a symptom-driven strategy of as-required ICS+SABA was compared to guideline-based titration of ICS therapy (Calhoun et al., 2012). This trial also included a third comparator group, where maintenance ICS therapy was adjusted based on exhaled

nitric oxide (FeNO). Patients were provided multiple blinded inhalers, and those in the symptom-driven group were asked to take two actuations of ICS every time they used two actuations of salbutamol for relief of symptoms.

Both the time to treatment failure and asthma exacerbation rates were not significantly different between all three groups. Asthma symptoms were also not significantly different between groups. Patients randomised to the symptom-driven group had significantly lower average monthly ICS doses compared to both other groups. These findings indicate that symptom-driven ICS+SABA therapy may be considered as an alternative treatment approach to conventional maintenance asthma therapy.

Two issues regarding the generalisability of the findings from this trial (Calhoun et al., 2012) require consideration. Firstly, median adherence to treatment in the trial was over 95%, which may be greater than that which occurs in the clinical setting (Haynes et al., 2008). Additionally, as the ICS and SABA treatments in the symptom-driven group were provided in separate inhalers, the benefits of this approach may have been underestimated, compared to patients in whom symptom-driven treatment can be provided in a single combination inhaler, whereby a dose of ICS is delivered whenever the inhaler is used for relief of symptoms.

1.10 Use of as-needed ICS/LABA therapy in mild asthma

The SOMA trial compared treatment with as-needed budesonide/formoterol with as-needed formoterol in mild asthma patients (Haahtela et al., 2006). FeNO was significantly reduced in the as-needed combination inhaler group. This study was not powered to assess impact on asthma exacerbations, and further interpretation is limited by the lack of a comparator group treated with regular ICS.

1.11 Rationale for combination ICS/LABA inhaler therapy

The preferred method to deliver ICS and LABA therapy is via a combination ICS/LABA inhaler (SIGN/BTS, 2012). Treatment with combination inhaler therapy is likely to be beneficial from two perspectives. It may encourage improved adherence with ICS (Marceau et al., 2006; Stoloff et al., 2004) and protect against LABA monotherapy (Morales et al., 2012; Barnes, 2002). Adherence to asthma therapy will be considered further.

1.11.1 Adherence to inhaled asthma therapy

The term ‘adherence’ refers to ‘the extent to which the patient’s behaviour matches agreed recommendations from the prescriber’ (Horne, 2006). This term implies shared decision-making and suggests a partnership between the patient and health-care provider in reaching an agreed treatment plan. Poor adherence to maintenance inhaled therapy can be defined using specific cut-offs; for example, less than 60% or

80% of prescribed doses taken. However, given that overuse of maintenance therapy or overuse of reliever therapy may also represent poor adherence, adherence is more accurately described as a spectrum of use and with differing patterns of treatment use, which may vary over time (Foster, Lavoie and Boulet, 2011).

Poor adherence to ICS therapy is common amongst asthma patients (Williams et al., 2007; Bender, Pedan and Varasteh, 2006) and is a key factor associated with poor outcomes. Prior studies have demonstrated that poor adherence to ICS is associated with lower lung function as asthma severity increases (Kandane-Rathnayake et al., 2009), increased risk of Emergency Department (ED) visits for severe exacerbations (Williams et al., 2004) and fatal outcome (Suissa et al., 2000). The impact of poor adherence is particularly relevant in difficult-to-treat and severe asthma (Heaney and Horne, 2012).

Various strategies to improve adherence have been suggested (Haynes et al., 2008). Non-pharmacological methods include improved patient education, use of asthma self-management skills, closer follow-up and medication reminders (Boulet et al., 2012; Foster, Lavoie and Boulet, 2011). Pharmacological strategies include simplification of treatment regimens (for example, by reducing the number of inhalers) and the use of combination ICS/LABA therapy as a method to increase exposure to ICS (Boulet et al., 2012; Murphy et al., 2012; Stempel et al., 2005).

1.11.2 Asthma self-management plans

Written asthma self-management plans are a key component of the non-pharmacological management of asthma and their use is advocated in global asthma

guidelines (SIGN/BTS, 2012; GINA, 2011). Asthma self-management plans generally share some common features: they provide information on maintenance therapy during periods of good control; there is guidance on symptoms which signify worsening asthma and specific instructions as to how to adjust medication use in this setting; and information on when to seek urgent medical help (FitzGerald and Gibson, 2006; Holt et al., 2005). Peak-flow and symptom-based plans are equivalent in their effect (Gibson and Powell, 2004; Powell and Gibson, 2003).

The use of an asthma self-management plan with regular patient review is associated with an improvement in health outcomes for patients (Gibson et al., 2003). This is likely to be due to a combination of factors: increased adherence to maintenance therapy, improved recognition of deteriorating symptoms and earlier treatment with systemic corticosteroids in the setting of acute exacerbations (Beasley, Cushley and Holgate, 1989).

The provision of written asthma self-management plans, with access to both peak-flow and symptom-based versions, therefore represents conventional clinical practice and may be considered an important feature of a real-world study. Given that peak-flow and symptom-based plans provide similar benefits, patients could be supported in continuing with their pre-study self-management strategy. In addition, use of asthma self-management education incorporating inhaler technique training would also reflect optimal clinical practice.

1.11.3 Therapeutic options with inhaled combination budesonide/formoterol

Combination budesonide/formoterol therapy has been studied with three patterns of use: fixed maintenance dosing with SABA as a reliever; adjustable maintenance dosing (AMD) with SABA as a reliever; and as maintenance and reliever therapy (SMART). These will be considered in turn.

1.12 Fixed maintenance budesonide/formoterol dosing with SABA for relief

Combination budesonide/formoterol treatment reduces exacerbation rates and improves PEFR, FEV_1 and asthma control compared with ICS alone (Noonan et al., 2006; Bateman et al., 2003; Buhl et al., 2003; Lalloo et al., 2003; Tal et al., 2002). The combination of budesonide/formoterol is also effective in improving PEFR and asthma symptoms when compared with budesonide plus formoterol delivered via separate inhalers (Noonan et al., 2006; Zetterstrom et al., 2001), and provides sustained bronchodilation for at least 24 hours when administered on a single occasion (Masoli et al., 2006). Fixed-dose budesonide/formoterol MDI is comparable to fixed-dose fluticasone/salmeterol in protecting against asthma exacerbations and improving asthma symptoms and lung function (Busse et al., 2008).

1.13 Adjustable maintenance dosing with SABA for relief

1.13.1 Increasing the dose of ICS during worsening asthma

There is conflicting evidence as to the beneficial effect of temporarily increasing the dose of ICS during an exacerbation (FitzGerald et al., 2004; Foresi, Morelli and Catena, 2000). Although doubling the dose of ICS in worsening asthma does not appear to reduce asthma exacerbations (Harrison et al., 2004), there is evidence to suggest that quadrupling the dose may be effective in preventing exacerbations (Oborne et al., 2009; Foresi et al., 2000). In addition, increasing the frequency of ICS dosing from two to four times a day, whilst maintaining the same total daily dose, is beneficial in unstable asthma (Toogood et al., 1982).

Furthermore, treatment with high-dose ICS (for example, 400µg every 30 minutes for two hours) is effective in improving PEFR and FEV_1 in acute asthma compared to systemic corticosteroids (Rodrigo, 2005; Rodrigo and Rodrigo, 1998). Thus, an increase in ICS dosing frequency combined with an asthma self-management plan may have a role in improving outcomes in worsening asthma.

This concept can be incorporated into an adjustable maintenance dosing plan that allows the patient to alter their ICS/LABA therapy based on their symptoms or PEFR. Thus, patients may use low medication doses (e.g. one inhalation twice daily) during periods of well-controlled asthma and increase their maintenance therapy in response to worsening symptoms (e.g. to four inhalations twice daily). Relief of symptoms is still provided by use of a SABA.

1.13.2 Budesonide/formoterol AMD plans

Studies comparing budesonide/formoterol prescribed as AMD or as fixed-dose therapy have demonstrated that AMD may reduce asthma exacerbations and improve asthma control, at lower overall medication doses (Aalbers et al., 2004; Ind et al., 2004; FitzGerald et al., 2003).

1.14 Primary SMART studies

The primary SMART studies refer to the seven large-scale studies which compared the budesonide/formoterol SMART regimen with the following treatments: double fixed-dose budesonide (Rabe et al., 2006b; Scicchitano et al., 2004) and quadruple fixed-dose budesonide (O'Byrne et al., 2005) for maintenance therapy, with terbutaline for relief; same fixed-dose budesonide/formoterol with terbutaline (Rabe et al., 2006a; O'Byrne et al., 2005) or formoterol (Rabe et al., 2006a) for relief; higher fixed-dose budesonide/formoterol with terbutaline for relief (Kuna et al., 2007); and fixed-dose fluticasone/salmeterol with terbutaline (Bousquet et al., 2007; Kuna et al., 2007) or salbutamol (Vogelmeier et al., 2005) for relief.

These studies are discussed in terms of their efficacy outcomes related to asthma exacerbations. The effect of the SMART regimen on asthma symptoms, lung function and reliever medication use are also summarised. The key features and outcomes from these studies are shown in Tables 1.2, 1.3, 1.4 and 1.5.

Table 1.2: Efficacy of the SMART regimen on asthma exacerbations (A)

Study	Maintenance treatment (µg) *	PRN reliever	Number of patients	Mean daily budesonide dose (µg) †	Time to first SE (SMART *v* comparators)	Severe exacerbations
Scicchitano 2004 (STEP)	B/F (2 x 200/6 od)	B/F (200/6)	947	583	Prolonged (p<0.001)	170 (18%) ‡ [HR (95% CI) 0.61 (0.50 to 0.74), p<0.001]
	B (400 bd)	Terbutaline	943	800		259 (27%) ‡
O'Byrne 2005 (STAY)	B/F (100/6 bd)	B/F (100/6)	925	300	Prolonged *v* both other groups (p<0.001)	0.36 § [HR (95% CI) 0.53 (0.44 to 0.65), p<0.001 *v* B/F+T)
	B/F (100/6 bd)	Terbutaline	909	200		0.68 §
	B (400 bd)	Terbutaline	926	800		0.68 §
Rabe 2006b (STEAM)	B/F (2 x 100/6 od)	B/F (100/6)	355	300	Not stated	0.08 § (p<0.001)
	B (400 od)	Terbutaline	342	400		0.35 §
Rabe 2006a (SMILE)	B/F (200/6 bd)	B/F (200/6)	1113	604	Prolonged *v* both groups (p=0.0048 *v* F and p<0.0001 *v* T)	0.19 § [HR (95% CI) 0.52 (0.44 to 0.63), p<0.0001 *v* B/F+T]
	B/F (200/6 bd)	F (6)	1140	400		0.29 §
	B/F (200/6 bd)	Terbutaline	1141	400		0.37 §

*: metered dose at randomisation; †: metered dose used during study period; ‡: number of participants (% of group) with event; §: events/patient/year; *v*: versus; HR: hazard ratio; B: budesonide; F: formoterol; T: terbutaline; od: once daily; bd: twice daily; SE: severe exacerbation; PRN: 'as-required'.

Table 1.3: Efficacy of the SMART regimen on asthma exacerbations (B)

Study	Maintenance treatment (µg) *	PRN reliever	Number of patients	Mean daily budesonide dose (µg) †	Time to first SE (SMART *v* comparators)	Severe exacerbations
Vogelmeier 2005 (COSMOS)	B/F (2 x 200/6 bd) ‡	B/F (200/6)	1067	816	Prolonged (p=0.0051)	0.24 § (p=0.0025)
	FL/SM (250/50 bd) ‡	Salbutamol	1076	583 ‖		0.31 §
Kuna 2007 (COMPASS)	B/F (200/6 bd)	B/F (200/6)	1107	604	Prolonged *v* both groups (p=0.023 *v* B/F+T and p=0.0034 *v* FL/SM+T)	0.24 § (p=0.0048 *v* B/F+T and p<0.001 *v* FL/SM+T)
	B/F (400/12 bd)	Terbutaline	1105	800		0.32 §
	FL/SM (2 x 125/25 bd)	Terbutaline	1123	500 ‖		0.38 §
Bousquet 2007 (AHEAD)	B/F (2 x 200/6 bd)	B/F (200/6)	1154	990	HR 0.82, p=0.12	0.25 § (p=0.039)
	FL/SM (500/50 bd)	Terbutaline	1155	1000 ‖		0.31 §

*: metered dose at randomisation; †: metered dose used during study period; ‡: maintenance dose titration allowed; §: events/patient/year; ‖: daily fluticasone dose; *v*: versus; HR : hazard ratio; B: budesonide; F: formoterol; FL: fluticasone; SM: salmeterol; od: once daily; bd: twice daily; PRN: 'as-required'.

Table 1.4: Efficacy of the SMART regimen on asthma control, reliever use and lung function (A)

Study	Maintenance treatment (µg)*	PRN reliever	Asthma control (% days)	Mean reliever use (inhs/day)	Mean treatment morning PEFR (L/min)	Mean treatment FEV_1 (L)
Scicchitano 2004 (STEP)	B/F (2 x 200/6 od)	B/F (200/6)	38.3 (p<0.001)	0.90 (p<0.001)	372 (p<0.001)	2.54 (p<0.001)
	B (400 bd)	Terbutaline	29.3	1.42	348	2.45
O'Byrne 2005 (STAY)	B/F (100/6 bd)	B/F (100/6)	45 (NS *v* B/F+T; p<0.001 *v* B+T)	0.73 (p<0.001 *v* both grps)	355 (p<0.001 *v* both grps)	2.51 (p<0.001 *v* B/F+T)
	B/F (100/6 bd)	Terbutaline	44	0.84	346	2.43
	B (400 bd)	Terbutaline	37	1.03	339	2.41
Rabe 2006b (STEAM)	B/F (2 x 100/6 od)	B/F (100/6)	47.4 (p=0.0012)	1.04 (p<0.001)	379 (p<0.001)	0.210 † (p<0.001)
	B (400 od)	Terbutaline	38.8	1.48	345	0.062 †
Rabe 2006a (SMILE)	B/F (200/6 bd)	B/F (200/6)	-0.63 ‡ (p<0.0001 *v* B/F+T; p=0.0009 *v* B/F+F)	-0.84 † (p<0.0001 *v* both grps)	15.3 † (p<0.0001 *v* B/F+T; p=0.004 *v* B/F+F)	0.06 † (p<0.0001 *v* B/F+T; p=0.00014 *v* B/F+F)
	B/F (200/6 bd)	F (6)	-0.53 ‡	-0.67 †	10.6 †	0.01 †
	B/F (200/6 bd)	Terbutaline	-0.49 ‡	-0.64 †	7.9 †	-0.02 †

*: metered dose at randomisation; †: treatment change from run-in; ‡: mean change in ACQ-5 score from baseline; inhs: inhalations; *v*: versus; NS = not statistically significant; B: budesonide; F: formoterol; T: terbutaline; od: once daily; bd: twice daily; PEFR: peak expiratory flow rate; L: litre; grps: groups; PRN: 'as-required'.

Table 1.5: Efficacy of the SMART regimen on asthma control, reliever use and lung function (B)

Study	Maintenance treatment (µg)*	PRN reliever	Asthma control (% days)	Mean reliever use (inhs/day)	Mean treatment morning PEFR (L/min)	Mean treatment FEV_1 (L)
Vogelmeier 2005 (COSMOS)	B/F (2 x 200/6 bd) §	B/F (200/6)	-0.64 ‡ (p=0.069)	0.58 (p<0.001)	Not reported	0.17 †‖ (p=0.066)
	FL/SM (250/50 bd) §	Salbutamol	-0.58 ‡	0.93	Not reported	0.14 †‖
Kuna 2007 (COMPASS)	B/F (200/6 bd)	B/F (200/6)	-0.85 ‡ (NS *v* both grps)	1.02 (NS *v* both grps)	363 (NS *v* both grps)	2.69 (NS *v* both grps)
	B/F (400/12 bd)	Terbutaline	-0.86 ‡	1.05	362	2.66
	FL/SM (2 x 125/25 bd)	Terbutaline	-0.90 ‡	0.96	367	2.67
Bousquet 2007 (AHEAD)	B/F (2 x 200/6 bd)	B/F (200/6)	-0.76 ‡ (p=0.59)	0.95 (p=0.36)	359 (p=0.67)	2.52 (NS)
	FL/SM (500/50 bd)	Terbutaline	-0.77 ‡	1.01	359	2.49

*: metered dose at randomisation; †: treatment change from run-in; ‡: mean change in ACQ-5 score from baseline; §: maintenance dose titration allowed; ‖:Pre-bronchodilator; NS = not statistically significant; inhs: inhalations; *v*: versus; B: Budesonide; F: Formoterol; T: Terbutaline; FL: Fluticasone; SM: Salmeterol; od: once daily; bd: twice daily; PEFR: peak expiratory flow rate; L: litre; grps: groups; PRN: 'as-required'.

1.14.1 SMART versus higher fixed-dose budesonide with terbutaline for relief

In a double-blind trial, patients were randomised to two actuations per day of 200/6µg budesonide/formoterol as maintenance (400/12µg per day total) with extra doses for relief (the SMART group) or 800µg per day of budesonide with terbutaline for relief (Scicchitano et al., 2004). This study recruited symptomatic patients with asthma with a recent exacerbation and used diary cards to record medication use. Patients were required to demonstrate bronchodilator reversibility to terbutaline at baseline. Patients with high reliever medication use (greater than 10 reliever actuations per day) and those with frequent asthma exacerbations (three or more courses of systemic corticosteroids in the prior six months) were excluded from study entry. Average baseline ICS dose was approximately 750µg per day.

Time to first severe exacerbation was significantly prolonged in the SMART group and there was a significant 39% reduction in the risk of a severe exacerbation with the SMART regimen (Table 1.2). There were a significantly greater proportion of asthma control days in patients on the SMART regimen (Table 1.4). Reliever overuse (defined as greater than 10 budesonide/formoterol inhalations per day) occurred in 2% of patients in the SMART group.

In another double-blind study, patients were randomised to one of three treatment groups: two actuations per day of 100/6µg budesonide/formoterol as maintenance (200/12µg per day total) with extra doses for relief (the SMART group); 800µg per day of budesonide with terbutaline for relief (fourfold higher budesonide group); or two actuations per day of 100/6µg budesonide/formoterol as maintenance (200/12µg per day total) with terbutaline for relief (fixed-dose group) (O'Byrne et al., 2005).

Eligible patients had a history of one or more asthma exacerbations in the preceding year and were symptomatic during run-in. Patients were required to demonstrate bronchodilator reversibility. Patients with high baseline reliever use, defined as 10 or more reliever inhalations in a day, were excluded. Average baseline ICS dose was approximately 620µg per day in the SMART and budesonide groups and 28% of the patients were on LABAs at baseline. Medication use was self-reported in diary cards.

Comparing SMART with four-fold higher budesonide treatment, the time to first severe exacerbation was significantly prolonged by treatment with the SMART regimen (Table 1.2). There was a significant 47% reduction in severe asthma exacerbations in the SMART group compared to the budesonide group. There were a significantly greater proportion of asthma control days in the SMART group (Table 1.4).

Rabe et al. (2006b) randomised patients to two actuations per day of 100/6µg budesonide/formoterol as maintenance (200/12µg per day total) with extra doses for relief (the SMART group) or 400µg of budesonide per day with terbutaline for relief. This study required patients to demonstrate bronchodilator reversibility or peak flow variability at baseline and used diary cards to record medication use. Patients were symptomatic during run-in but did not have high baseline reliever use, defined as 10 or more inhalations per day. Average baseline ICS dose was approximately 430µg per day. 10% of patients randomised to the budesonide group were treated with LABAs prior to study entry.

Treatment with the SMART regimen reduced severe exacerbations requiring medical intervention by 76% (Table 1.2). There were a significantly greater proportion of asthma control days in the SMART group (Table 1.4). Reliever overuse, defined as greater than 10 as-needed budesonide/formoterol inhalations per day, occurred in 3% of patients in the SMART group.

Considered together, these studies demonstrated the superiority of the SMART regimen compared to higher fixed-dose budesonide therapy in reducing asthma exacerbations and improving asthma control. Studies in which the comparator groups were also treated with maintenance LABA therapy are now considered.

1.14.2 SMART versus same fixed-dose budesonide/formoterol with terbutaline or formoterol for relief

As discussed in the previous section, the study by O'Byrne et al. (2005) also compared SMART therapy with the same fixed-dose of budesonide/formoterol for maintenance with terbutaline for relief. Patients in the fixed-dose group were treated with 200/12µg of budesonide/formoterol per day. The baseline daily ICS dose in the fixed-dose group was approximately 600µg and 29% of the group used LABAs prior to study entry.

Treatment with the SMART regimen significantly prolonged the time to the first severe exacerbation and reduced severe exacerbations by 47% compared to fixed-dose therapy (Table 1.2). Treatment with the SMART regimen also significantly prolonged the time to second and third severe exacerbations compared to fixed-dose

therapy. There was no significant difference between groups in the proportion of asthma control days (Table 1.4). FEV_1 was significantly higher in the SMART group (Table 1.4). As the minimal clinically important difference for FEV_1 may be between 100 to 200ml (Tepper et al., 2012), the absolute difference of 80ml between groups can be considered of borderline clinical significance. There were fewer days of high reliever use, defined as greater than eight reliever inhalations per day, in the SMART group (26 episodes in 925 participants in the SMART group versus 142 episodes in 909 participants in the fixed-dose group). Mean budesonide exposure was approximately 100µg per day higher in the SMART group.

This study suggested that treatment with the SMART regimen was superior to the same fixed-dose budesonide/formoterol treatment (with SABA for relief) in reducing asthma exacerbations and that SMART may be of particular benefit in patients with repeated exacerbations.

In another double-blind trial, patients were randomised to one of three treatment regimens: two actuations per day of 200/6µg budesonide/formoterol as maintenance (400/12µg per day total) with extra doses for relief (the SMART group); two actuations per day of 200/6µg budesonide/formoterol as maintenance (400/12µg per day total) with terbutaline for relief (terbutaline as-needed group); or two actuations per day of 200/6µg budesonide/formoterol as maintenance (400/12µg per day total) with 6µg formoterol for relief (formoterol as-needed group) (Rabe et al., 2006a).

Patients were required to demonstrate bronchodilator reversibility at baseline and had suffered at least one severe asthma exacerbation in the preceding year. As

previously, patients were symptomatic during run-in but were excluded if they used more than 10 reliever inhalations in a day. The patients in this study had poorly-controlled asthma at baseline, as measured by an Asthma Control Questionnaire (ACQ)-5 score of 1.9 at baseline. Baseline ICS dose was approximately 760µg per day across the three groups and 60% of patients were on LABAs pre-study. Medication use was measured by diary cards.

Treatment with the SMART regimen significantly prolonged the time to first severe exacerbation compared to both the formoterol and terbutaline as-needed groups (Table 1.2). Severe exacerbations were significantly reduced by 33% with SMART compared to formoterol as-needed and by 48% compared with terbutaline as-needed. Severe exacerbations requiring an ED visit or hospital admission were also significantly reduced by 27% with the SMART regimen compared with formoterol as-needed and by 39% compared with terbutaline as-needed.

ACQ-5 scores were significantly lower in the SMART group compared to both the other treatment groups (Table 1.4), reflecting a greater improvement in asthma control. FEV_1 was significantly higher in the SMART group compared to both the other treatment groups (Table 1.4), though the difference between the SMART and comparator groups, of approximately 50ml to 80ml, may not be of clinical significance (Tepper et al., 2012). High reliever medication use was reduced in the SMART group, with 70/1107 (6.3%) and 130/1138 (11.4%) of patients in the SMART and terbutaline as-needed groups respectively using four or more reliever inhalations on more than 100 study days. In a sub-group analysis of this study, the risk of high reliever use (defined as greater than six inhalations per day) was

significantly reduced by 49% with SMART compared to terbutaline as-needed (Buhl et al., 2012). Mean budesonide dose was approximately 200µg per day higher in the SMART group.

This trial also provided data regarding the efficacy of formoterol as a reliever treatment compared to terbutaline as a reliever, in patients on maintenance budesonide/formoterol therapy. In keeping with prior studies (Pauwels et al., 2003b; Tattersfield et al., 2001), patients randomised to formoterol as-needed had significantly fewer asthma exacerbations. This finding indicates that the reduction in severe exacerbations observed with the SMART regimen is partly attributable to the as-needed formoterol component of the treatment plan and also suggests that there is an added benefit of the combination of budesonide/formoterol as a reliever, above that provided by formoterol as a reliever alone.

These two studies (Rabe et al., 2006a; O'Byrne et al., 2005) had several key limitations which affect their generalisability to clinical practice. Firstly, patients with high baseline reliever medication use were excluded from study entry. Secondly, patients were required to demonstrate significant bronchodilator reversibility. Thirdly, patients were selected on the basis of having asthma symptoms during run-in and a history of prior asthma exacerbations. However, patients subsequently randomised to the fixed-dose budesonide/formoterol comparator groups then had an ICS dose reduction. This led to the criticism that these patients were symptomatic but not on an appropriate level of maintenance therapy (Cates and Lasserson, 2009), thereby not reflecting current clinical practice

guidelines which recommend a treatment intensity appropriate to the level of asthma control (SIGN/BTS, 2012; GINA, 2011).

Thus, the findings from these two studies (Rabe et al., 2006a; O'Byrne et al., 2005) have limited generalisability to the 'real-world' use of the SMART regimen. These studies (Rabe et al., 2006a; O'Byrne et al., 2005) also suggest that the reduction in severe asthma exacerbations with the SMART regimen is at the cost of higher ICS exposure.

1.14.3 SMART versus higher fixed-dose budesonide/formoterol with terbutaline for relief

The study by Kuna et al. (2007) was designed to test the hypothesis that the SMART regimen may be as effective as higher fixed-dose maintenance ICS/LABA therapy. Patients were randomised to one of three treatment regimens: two actuations per day of 200/6µg budesonide/formoterol as maintenance (400/12µg per day total) with extra doses for relief (the SMART group); two actuations per day of 400/12µg budesonide/formoterol as maintenance (800/24µg per day total) with terbutaline for relief (higher fixed-dose budesonide/formoterol group); or two actuations per day of 125/25µg fluticasone/salmeterol as maintenance with terbutaline for relief (fixed-dose fluticasone/salmeterol group).

In keeping with the design of the studies discussed above, patients were required to demonstrate bronchodilator reversibility at baseline and were excluded if they had high baseline reliever medication use. Baseline ICS dose was approximately 750µg per day across the three groups and 50% of patients were on LABAs pre-study.

In the comparison between SMART and higher fixed-dose budesonide/formoterol, treatment with the SMART regimen significantly prolonged the time to first severe exacerbation and significantly reduced severe exacerbations by 28% (Table 1.3). The improvement in ACQ-5 scores and lung function was not significantly different between these two groups (Table 1.5).

The reduction in severe asthma exacerbations in the SMART group was achieved with 25% lower ICS exposure compared to the fixed-dose budesonide/formoterol group. This finding suggests that self-titrated increasing budesonide/formoterol use by patients on the SMART regimen in response to worsening symptoms may contribute to the greater efficacy in reducing asthma exacerbations.

1.14.4 SMART versus fixed-dose salmeterol/fluticasone with terbutaline or salbutamol for relief

In the study by Kuna et al. (2007) described in the previous section, treatment with the SMART regimen was also compared with fixed-dose fluticasone/salmeterol with terbutaline as a reliever.

SMART therapy significantly prolonged the time to the first severe exacerbation compared to fluticasone/salmeterol (Table 1.3), with a significant 39% reduction in severe exacerbations. ACQ-5 score and lung function were not significantly different between these two groups (Table 1.5).

In the comparison between the fixed-dose budesonide-formoterol group and the fixed-dose fluticasone/salmeterol group, there was no significant difference in the time to first severe exacerbation or the rate of severe exacerbations.

The findings from this study (Kuna et al., 2007) suggest that the as-needed use of budesonide/formoterol with the SMART regimen is an important contributing factor in reducing severe asthma exacerbations, rather than the actual nature of the component products within a fixed-dose combination treatment regimen.

In an open-label real-world study, patients were randomised to two actuations twice daily of 200/6µg of budesonide/formoterol as maintenance (800/24µg per day total) with extra doses for relief (the SMART group) or two actuations per day of 250/50µg fluticasone/salmeterol as maintenance with salbutamol for relief (fixed-dose fluticasone/salmeterol group) (Vogelmeier et al., 2005). Maintenance dose titration according to asthma control was permitted in both groups. The protocol did not require reversibility testing for eligibility and patients were also not required to keep daily diaries in an effort to reflect the real-world situation.

The time to first severe exacerbation was significantly prolonged in patients on the SMART regimen and there was a significant 22% reduction in severe exacerbations (Table 1.3). In keeping with prior findings (Kuna et al., 2007), asthma symptoms and lung function were not significantly different between the two groups (Table 1.5).

In another study, patients were randomised to two actuations twice daily of 200/6µg of budesonide/formoterol as maintenance (800/24µg per day total) with extra doses for relief (the SMART group) or two actuations per day of 500/50µg fluticasone/salmeterol as maintenance with terbutaline for relief (fixed-dose fluticasone/salmeterol group) (Bousquet et al., 2007). The comparator group were therefore on a higher maintenance dose of ICS compared to the two studies discussed previously (Kuna et al., 2007; Vogelmeier et al., 2005). Patients with high baseline reliever use were excluded. Daily diaries were used to record medication use.

Time to the first severe exacerbation was not significantly different between the two groups, although there was a significant 21% reduction in the rate of severe exacerbations in the SMART group (Table 1.3). ACQ-5 scores and lung function were not significantly different between the groups (Table 1.5).

This study also analysed the relationship between a day of high reliever use and the subsequent development of severe asthma exacerbations. Treatment with the SMART regimen was associated with a significant 41% reduction in the rate of severe exacerbations occurring in the 28 days after a day of high reliever use, defined as a day of greater than four reliever inhalations. This suggests that the as-needed use of budesonide/formoterol in response to worsening symptoms may contribute to the reduction in severe exacerbations observed with the SMART regimen. However, the interpretation of these findings is limited by the imprecision of self-report as a measure of medication use. This issue will be discussed in more detail in later sections.

1.15 The budesonide/formoterol SMART regimen and asthma control

1.15.1 Asthma control measurements

One of the criticisms (Chapman et al., 2010) of the SMART clinical trial programme is that a number of the studies reported differing components of asthma control (e.g. night-time awakenings, symptom-free days, or reliever-free days) separately (Rabe et al., 2006b; O'Byrne et al., 2005; Scicchitano et al., 2004), thus limiting interpretations of the impact of the SMART regimen on asthma control. Four studies (Bousquet et al., 2007; Kuna et al., 2007; Rabe et al., 2006a; Vogelmeier et al., 2005) did however use the ACQ-5 as a validated composite score of asthma control.

In order to overcome this criticism, post-hoc analyses have suggested that the SMART regimen is comparable to conventional treatment regimens in achieving controlled or partly-controlled asthma, as defined by the Global Initiative for Asthma (GINA) (Bateman et al., 2010).

1.15.2 Dissociation between asthma control and asthma exacerbations

It is interesting to observe that treatment with the SMART regimen is associated with a reduction in severe exacerbations, but with lesser impact on improving day-to-day asthma control compared to fixed-dose budesonide/formoterol with terbutaline for relief. In order to suggest possible explanations for this observation, it is necessary to define asthma control and asthma exacerbation.

Asthma control may be divided into periods of clinical control ('stable asthma'), deteriorating control and clinical exacerbation (Reddel et al., 1999; Tattersfield et al., 1999). During periods of stable asthma, symptoms may be relatively infrequent and reliever medication use may be stable at a low or minimal level (Reddel et al., 1999; Cockcroft and Swystun, 1996). During periods of deteriorating control, symptoms may increase, together with an increase in reliever medication use and increased PEFR variability (Reddel et al., 1999; Tattersfield et al., 1999). Asthma exacerbations may be characterised by a peak in asthma symptoms and reliever use, followed by a gradual improvement (Reddel et al., 1999; Tattersfield et al., 1999).

There may, however, be dissociation in the relationship between asthma control and asthma exacerbations and in clinical practice, these periods may not be as well defined as described above.

In support of this concept, in the FACET study (Pauwels et al., 1997), severe exacerbations were reduced to a greater extent by a fourfold higher ICS dose than by the addition of a LABA to low-dose ICS. However, episode-free days, which were a marker of well-controlled asthma, were significantly increased by the addition of LABA to low-dose ICS, but not by treatment with fourfold higher ICS dose. This suggests that treatment regimens may have differing impact on asthma symptoms and asthma exacerbations.

Further evidence for the dissociation between asthma control and exacerbations comes from the study by Papi et al. (2007) discussed previously. Patients in the symptom-driven treatment group (as-needed ICS/SABA inhaler) and regular

combination treatment group (regular ICS/SABA inhaler with SABA for relief) had similar improvements in asthma symptom scores during the study. However, significantly fewer asthma exacerbations occurred in the as-needed group.

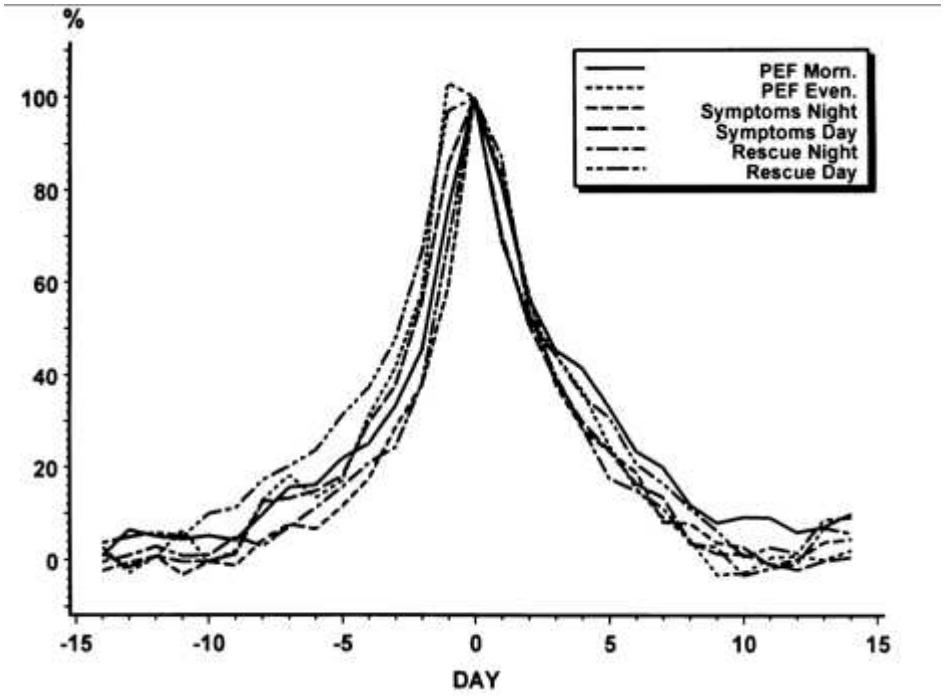
Considered together, the dissociation between asthma control and asthma exacerbations may be one explanation for the observation that treatment with the SMART regimen is effective in reducing severe exacerbations, and has lesser impact in improving day-to-day asthma control compared to the same fixed-dose of budesonide/formoterol with SABA for relief.

1.16 Possible mechanisms for the reduction in severe exacerbations with the SMART regimen

1.16.1 Altering the time course and severity of an asthma exacerbation

The findings from the FACET study (Tattersfield et al., 1999; Pauwels et al., 1997) suggest that asthma exacerbations develop over seven-to-ten days, over which time asthma symptoms gradually worsen and reliever medication use increases. This occurs gradually from 10 days prior to an exacerbation and then more rapidly in the five days preceding the exacerbation (Figure 1.1). This may provide a 'window of opportunity' of five to 10 days of worsening symptoms (Lindmark, 2008), during which increasing anti-inflammatory and bronchodilator therapy with budesonide/formoterol in response to worsening symptoms may alter the progression of, and potentially prevent, the development of severe exacerbations.

Figure 1.1: Time course of an asthma exacerbation



Change in symptoms, peak flow and reliever medication use in the 14 days pre and post severe asthma exacerbations (Day 0). Data has been standardised and expressed as a % change from Day -14. [Reprinted with permission from the American Thoracic Society. Copyright © 2012 American Thoracic Society. Figure 2: (Tattersfield et al., 1999) Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med,* 160 (2), 594-599. Official journal of the American Thoracic Society.]

There is indirect evidence for this hypothesis from sub-group analyses (Buhl et al., 2012) of severe exacerbations occurring in a 21 day 'window' after an episode of high reliever medication use, in patients randomised to SMART (400/12µg maintenance per day) or the same fixed-dose budesonide/formoterol for maintenance with terbutaline for relief. Following an episode of high reliever use, defined as greater than six reliever inhalations per day, there was a non-significant 45% reduction in severe exacerbations occurring in the subsequent 21 days with the

SMART regimen compared to the fixed-dose regimen. During this period, average ICS dose was almost three times higher in the SMART group (1363µg per day versus 500µg per day).

These findings suggest that the increased use of budesonide/formoterol during periods of worsening asthma may affect the development of subsequent severe exacerbations.

1.16.2 Possible pharmacological effects of high-dose budesonide and formoterol therapy during worsening asthma

The precise mechanisms by which increasing budesonide/formoterol use during worsening asthma attenuates the progression of the exacerbation are uncertain, but several possibilities are suggested (Barnes, 2007).

Use of repeated multiple doses of ICS has substantial efficacy in reducing hospital admission rates in acute asthma, possibly due to topical effects of ICS on airway vasculature (Rodrigo, 2006). The decrease in airway blood flow following treatment with inhaled budesonide may help to reduce airway inflammation in acute asthma (Mendes et al., 2003). This 'non-genomic' effect of ICS therapy may be rapid in onset and have a dose-response relationship (Rodrigo, 2006).

Formoterol has substantial efficacy as a bronchodilator in acute asthma (Rodrigo et al., 2010). The dose-dependent prolonged bronchodilator efficacy of formoterol (Derom and Pauwels, 1992) may provide time for the genomic anti-inflammatory effects of ICS (Rodrigo, 2006). In addition, there is some evidence that treatment

with formoterol may have anti-inflammatory effects that contribute to its clinical efficacy (Reddel et al., 2011; Gravett et al., 2010; Ketchell et al., 2002). The combination of budesonide and formoterol may also act synergistically (Roth et al., 2002; Anderson, 2000).

These findings suggest that increasing use of budesonide/formoterol during worsening asthma may provide an additive beneficial effect on airway inflammation and bronchodilation.

1.16.3 Increasing exposure to ICS in poorly adherent patients

Use of a combination budesonide/formoterol inhaler for both maintenance and relief may increase exposure to ICS in patients poorly adherent to maintenance therapy, as patients would receive a dose of ICS whenever they used their inhaler for symptomatic relief. This increase in ICS dose may translate to a reduction in severe exacerbations.

A real-world RCT of SMART versus ICS (plus SABA) therapy in poorly adherent asthma patients in primary care supports this hypothesis (Sovani et al., 2008). Average daily budesonide dose was significantly increased by almost 200µg per day in the SMART group (Sovani et al., 2008), though this study was not powered to detect differences between groups in severe exacerbations.

1.17 Airway inflammation with the budesonide/formoterol SMART regimen

Two trials have investigated the impact of the SMART regimen on airway inflammation (Pavord et al., 2009; Sears et al., 2008).

In a sub-group analysis from a conventional best practice (CBP) study, Sears et al. (2008) compared sputum eosinophils in patients treated with the SMART regimen (mean ICS dose of 748µg per day during the study) or CBP (mean ICS dose of 1015µg per day during the study). Sputum eosinophils decreased with treatment in both groups and there was no significant difference between the groups. The authors concluded that the SMART regimen produces comparable effects on airway inflammation compared to guideline-based care.

In a study comparing the SMART regimen (mean 604/18µg dose per day during the study) with higher fixed-dose budesonide/formoterol treatment with terbutaline for relief (mean 1600/24µg dose per day during the study) over 52 weeks of treatment, there was a non-significant increase in sputum eosinophils in the SMART group from 1.6% to 1.9%, but a significant reduction in eosinophil counts in the fixed-dose group from 2.2% to 1.2% (Pavord et al., 2009). This resulted in a significant difference between groups in favour of the fixed-dose group. Biopsy eosinophils were also significantly higher in the SMART group. There were, however, no differences in clinical outcomes, including severe exacerbations, lung function or reliever medication use.

Concern has been raised that these findings may signal that the SMART regimen is associated with worsening airway inflammation compared to conventional fixed-dose asthma therapy (Chapman et al., 2010). However, it is important to note that all patients in the trial by Pavord et al. (2009) had asthma symptoms and reduced peak flow during run-in and that those randomised to the SMART regimen then had an ICS dose reduction (baseline dose of 741µg), whereas patients randomised to fixed-dose therapy had an ICS dose increase (baseline dose of 867µg). Whilst it can be concluded that a fixed four-fold higher dose of budesonide/formoterol is more effective than low-dose SMART in controlling airway inflammation under these conditions, this finding cannot be extrapolated to clinical practice, whereby ICS dose reduction in symptomatic patients is not advocated.

There is currently insufficient evidence to determine the long-term impact of the SMART regimen on airway inflammation when compared with the same fixed-dose of maintenance budesonide/formoterol therapy with SABA for relief.

1.18 Real-world budesonide/formoterol SMART studies

1.18.1 Conventional best practice (CBP) studies

A number of 'real-world' studies have been undertaken, comparing SMART with CBP (Riemersma, Postma and van der Molen, 2012; Quirce et al., 2011; Soes-Petersen et al., 2011; Louis et al., 2009; Sears et al., 2008). CBP was generally defined as any guideline-based asthma therapy, with the exception of SMART.

Participants in the SMART group typically could not have maintenance dose adjustments, whilst investigators were free to adjust therapy in the CBP group.

These studies were open-label in design, recruited mild to moderate asthma patients, and used daily dairies to record medication use. A recent prior asthma exacerbation was not a required entry criterion. In keeping with the real-world designs, participants were also not required to demonstrate bronchodilator reversibility and were not excluded on the basis of high baseline reliever medication use; however, smokers with a greater than 10 pack-year history were not eligible.

Participants had a baseline ACQ-5 score of approximately 1.3 to 1.4 and had higher lung function and lower baseline reliever use compared to patients in the SMART double-blind trials discussed previously.

A summary of the key efficacy findings are shown in Table 1.6. In contrast to the primary SMART studies, there was a lack of significant difference in severe exacerbations between the SMART and CBP groups (Table 1.6). Asthma symptoms, as measured by ACQ-5, were comparable or, in some cases, improved to a greater degree by the SMART regimen compared to CBP (Table 1.6). The principal findings were that ICS exposure was reduced and that there was a lower medication cost associated with treatment with the SMART regimen.

A pooled analysis of six CBP trials reported that the SMART regimen did not prolong the time to first severe exacerbation, but that there was a modest 15% reduction in severe exacerbations (Demoly et al., 2009).

Table 1.6: SMART conventional best practice studies

Study	Maintenance treatment *	Reliever treatment	Number of patients	Time to first SE HR (95% CI): SMART versus comparator	Rate of SE, events/patient/year [RR (95% CI)]	ACQ-5 score: SMART versus comparator (95% CI)
Riemersma 2012	B/F (2 x 100/6 od)	B/F (100/6)	54	-	16.4 (p=0.80) ‡	-0.06 (-0.3 to 0.2), p=0.67
	CBP †	Non-SMART	48		16.8 ‡	
Quirce 2011	B/F (200/6 bd) †	B/F (200/6)	328	0.748 (0.433 to 1.292), p=0.2974	0.16 [0.753 (0.44 to 1.26)], p=0.2869	-0.12 (-0.23 to -0.01), p=0.0292
	CBP †	Non-SMART	326		0.22	
Soes-Petersen 2011	B/F (200/6 bd)	B/F (200/6)	931	0.79 (0.56 to 1.12), p=0.189	0.16 [0.74 (0.54 to 1.01)], p=0.058	-0.09 (-0.15 to -0.03), p=0.003
	CBP †	Non-SMART	923		0.22	
Louis 2009	B/F (200/6 bd)	B/F (200/6)	450	HR not provided, p=0.75	0.074 (p=0.09)	-0.12 (-0.20 to 0.04), p=0.0026
	CBP †	Non-SMART	458		0.13	
Sears 2008	B/F (200/6 bd)	B/F (200/6)	772	0.99 (0.70 to 1,41), p=0.95	0.19 [0.92 (0.67 to 1.28)], p=0.63	1.27 to 1.08 (p=0.46 for difference between groups)
	CBP †	Non-SMART	766		0.21	1.24 to 1.09

*: Metered dose in µg; † maintenance dose titration allowed; ‡ days of mild exacerbation per year; B/F: budesonide/formoterol via Turbohaler; od: once daily; bd: twice daily; SE: severe asthma exacerbation; HR: hazard ratio; RR: relative rate; CBP: conventional best practice (treatment with any guideline-based therapy, except SMART); ACQ-5: Asthma Control Questionaire-5 score.

Interestingly, the benefit of the SMART regimen in reducing exacerbations appeared to be more evident in patients who were at GINA Step 4 at study entry (i.e. likely to have more severe asthma) (Demoly et al., 2009). This finding is consistent with a post-hoc analysis of the SMART double-blind clinical trial programme (Bateman et al., 2011).

Though these studies were designed to replicate real-world practice, there are two limitations which affect their generalisability to the clinical setting. Firstly, as they were undertaken in patients with greater baseline control and lesser asthma severity than the primary SMART studies, it is not possible to determine if the SMART approach retains its efficacy benefit in reducing severe exacerbations in real-world patients with moderate to severe asthma, including patients at risk of severe exacerbations. Secondly, as the comparator CBP groups received a range of treatments, it is not possible to determine the differential efficacy of the SMART approach versus specific comparator regimens, such as the same fixed-dose of budesonide/formoterol maintenance therapy with SABA for relief.

1.18.2 Cost effectiveness studies

A number of analyses investigating the cost effectiveness of the treatments in the open-label trials have been performed (Goossens et al., 2009; Wickstrom et al., 2009; Miller and FitzGerald, 2008; Stallberg et al., 2008; Price, Wiren and Kuna, 2007; Lundborg et al., 2006). These have suggested that the direct costs (e.g. medication costs, healthcare visit costs) and indirect costs (e.g. loss of productivity due to sick days) are reduced with the use of the SMART regimen.

1.18.3 Future studies

A search of clinicaltrials.gov suggests that there are other real-world studies currently being undertaken or that have been recently completed (e.g. 'A comparison of Symbicort single inhaler therapy and conventional best practice for the treatment of persistent asthma [NCT00628758]'; 'Real life effectiveness of Symbicort maintenance and reliever therapy in asthma patients across Asia' [NCT00939341]). These studies may provide further data on the effectiveness of the SMART regimen in real-world settings.

1.19 Low versus high maintenance doses with the budesonide/formoterol SMART regimen

A large-scale real-world study compared the efficacy of 'low-dose' SMART treatment (200/6µg one actuation twice daily plus as-needed) versus 'high-dose' treatment (200/6µg two actuations twice daily plus as-needed) (Aubier et al., 2010). High-dose treatment significantly prolonged the time to first severe exacerbation. A significantly greater proportion of high-dose patients had an improvement of greater than 0.5 points on the ACQ-5 score, which is considered the threshold for clinical significance (Juniper et al., 2006). Reliever medication use was also significantly reduced by high-dose treatment. Low baseline lung function was a predictor of improved response with high-dose treatment.

In sub-group analyses of this trial, patients whose pre-study baseline ICS doses were ≥1600µg/day (with or without LABA) who were subsequently randomised to the

high-dose SMART regimen (800/24µg maintenance treatment per day) did not suffer any loss of asthma control (Aubier et al., 2011). High-dose SMART treatment also provided greater protection from asthma exacerbations in patients who smoked (van Schayck et al., 2012).

These findings indicate that in a clinical trial of the SMART regimen in real-world asthma patients at risk of severe exacerbations, which may include patients with low baseline lung function, high baseline ICS dose and patients who smoke, the use of 200/6µg two actuations twice daily (corresponding to BTS Step 3 or GINA Step 4) as the maintenance budesonide/formoterol dose may be considered the preferred option.

1.20 Systematic reviews and meta-analyses of trials of the SMART regimen

A number of systematic reviews of trials of the SMART regimen have been published (Lee and Corren, 2008; McCormack and Lyseng-Williamson, 2007). These have generally suggested that the SMART approach is advantageous in reducing severe exacerbations in patients with uncontrolled asthma and that this treatment strategy is well tolerated.

Three meta-analyses have investigated the efficacy and safety of the SMART regimen with comparator treatments of the same fixed-dose maintenance ICS/LABA treatment (Edwards et al., 2010; Agarwal et al., 2009; Cates and Lasserson, 2009) or higher fixed-dose ICS/LABA treatment (Edwards et al., 2010; Agarwal et al.,

2009) with SABA for relief in adult patients. A fourth meta-analysis (Sears and Radner, 2009) has specifically investigated the safety of the SMART regimen in clinical trials. A summary of the key results for the efficacy outcomes are shown in Table 1.7.

The meta-analyses confirmed that the SMART regimen reduces asthma exacerbations requiring corticosteroids compared to the same fixed-dose budesonide/formoterol therapy (with SABA for relief) (Table 1.7). A comprehensive analysis of the methodological processes used in the SMART clinical trial programme confirmed that this finding is consistent between trials, but highlighted the requirement for further data on the benefits and risks of this regimen in 'real-world' patients (Braido et al., 2011).

Table 1.7: Meta-analyses of the SMART studies in adults – efficacy

Study	Comparators	Number of trials included	Outcome	SMART *v* higher fixed-dose ICS: RR/OR (95% CI)	SMART *v* same fixed-dose B/F: RR/OR (95% CI)	SMART *v* higher fixed-dose B/F: RR/OR (95% CI)	SMART *v* higher fixed-dose FL/SM: RR/OR (95% CI)
Edwards 2010	Equivalent or up to fourfold higher maintenance ICS dose	6	a) Risk of severe exacerbations [oral corticosteroids for ≥3 days, emergency visit, and/or hospitalisation]	0.59 (0.51 to 0.68), p<0.00001	0.57 (0.49 to 0.66), p<0.00001	0.74 (0.58 to 0.96), p=0.02	0.76 (0.64 to 0.90), p=0.002
			b) Oral corticosteroids for asthma exacerbations	0.59 (0.50 to 0.68), p<0.00001	0.58 (0.49 to 0.67), p<0.00001	0.68 (0.51 to 0.90), p=0.008	0.75 (0.62 to 0.91), p=0.004
Cates 2009	Same fixed-dose ICS/LABA	2	a) Asthma exacerbations requiring hospitalisation	-	0.68 (0.40 to 1.16) *	-	-
			b) Oral corticosteroids for asthma exacerbations	-	0.54 (0.44 to 0.65) *	-	-
Agarwal 2009	Fixed-dose ICS or ICS/LABA or conventional best practice (CBP)	8	Odds of severe exacerbations [as defined by the individual trial protocols]	0.52 (0.45 to 0.61) *	0.65 (0.53 to 0.8) *		

*: p values not reported; *v*: versus; RR: relative risk or rate; OR: odds ratio; ICS: inhaled corticosteroid; B/F: budesonide/formoterol; FL/SM: fluticasone/salmeterol.

1.21 Regulatory approval for the budesonide/formoterol SMART regimen

In the United Kingdom, the SMART regimen is approved for patients who are poorly controlled on ICS alone (BTS Step 2) or as an alternative treatment plan for 'selected' patients on low to medium dose ICS and LABA (BTS Step 3) (SIGN/BTS, 2012). The GINA guidelines suggest that the SMART regimen may be used as an alternative to fixed low-dose ICS and LABA therapy (GINA Step 3) (GINA, 2011).

These guidelines do not recommend the use of the SMART regimen in patients who are uncontrolled at higher treatment steps, who may also be at risk of severe exacerbations. In addition, there are recommendations cautioning against the use of the SMART regimen in patients with high reliever medication use, poor adherence, or difficult to control asthma (Taylor et al., 2008). This may be as a consequence of concerns regarding the safety and efficacy of the SMART regimen in these 'real-world' patients.

The SMART regimen is approved for use with budesonide/formoterol via Turbohaler and not with budesonide/formoterol via MDI (AstraZeneca Limited, 2011a).

1.22 Maintenance and reliever treatment with beclometasone/formoterol combination MDI

A recently published trial has investigated the use of combination beclometasone/formoterol via MDI as part of a maintenance and reliever regimen in adult patients with asthma (Papi et al., 2013). In this double-blind study, patients

were randomised to receive 12 months of treatment with either two actuations per day of 100/6µg beclometasone/formoterol via MDI as maintenance (200/12µg per day total) with extra doses for relief (maintenance and reliever group) or the same dose of beclometasone/formoterol for maintenance with 100µg of salbutamol for relief (salbutamol as-needed group).

Patients were required to demonstrate bronchodilator reversibility at baseline, had at least one severe asthma exacerbation in the preceding year and were eligible if they were not fully controlled after two weeks of 200/12µg per day of beclometasone/formoterol during run-in. Baseline ACQ-7 score was approximately 1.9 in both groups. Average ICS dose at study entry was approximately 1130µg per day (beclometasone non-extrafine equivalent) and 80% of patients were on LABAs. Patients recorded their use of rescue medication on an electronic daily diary and were asked to contact study investigators if six rescue actuations per day for two consecutive days were used.

Treatment with the maintenance and reliever regimen significantly prolonged the time to first severe asthma exacerbation and significantly reduced severe exacerbations by 34%. Severe exacerbations requiring an ED visit or hospital admission were also significantly reduced by 33% with the SMART regimen.

These findings suggest that in addition to the use of budesonide/formoterol with the SMART regimen, other combination ICS/rapid-onset LABA inhaler preparations, including those delivered by MDI, may also be effective in reducing severe exacerbations in adults with moderate to severe asthma.

1.23 Inhaled formulations for budesonide/formoterol

Budesonide/formoterol at the 200/6µg dose is formulated as a Dry Powder Inhaler (DPI) (Symbicort Turbohaler) and as a heptafluoropropane (HFA) MDI (called 'Vannair' in New Zealand) (Lyseng-Williamson and Simpson, 2008; McCormack and Lyseng-Williamson, 2007). The Turbohaler formulation is registered for use in asthma in many countries including New Zealand, Australia, Canada and those of the European Union. As of 2013, the MDI formulation is registered for use in asthma in New Zealand, Australia, the USA and Switzerland (AstraZeneca Limited, 2011a). This MDI formulation is not available elsewhere in Europe (AstraZeneca Limited, 2011a).

1.24 Therapeutic equivalence for the MDI and Turbohaler budesonide/formoterol formulations

1.24.1 Pharmacokinetic comparisons

Systemic bioavailability of budesonide from the 200/6µg MDI formulation is comparable to that from the 200/6µg Turbohaler formulation in healthy volunteers (AstraZeneca Limited, 2011a). The Product Information for the MDI formulation states that 'Vannair 200/6µg MDI delivers the same amount of budesonide and formoterol as Symbicort Turbohaler 200/6µg' (AstraZeneca Limited, 2011b).

1.24.2 Long-term therapeutic equivalence

Two long-term safety and efficacy clinical trials have demonstrated the therapeutic equivalence of budesonide/formoterol via MDI and Turbohaler in adults (Morice et al., 2008; Morice et al., 2007).

1.24.3 Short-term therapeutic equivalence

To my knowledge, acute bronchodilator equivalence studies for budesonide/formoterol via MDI and Turbohaler have not been published. However, there is a comparable acute bronchodilator effect between budesonide/formoterol via MDI and formoterol via Turbohaler (Table 1.8) (Kaiser et al., 2008; Miller, Senn and Mezzanotte, 2008; Corren et al., 2007; Noonan et al., 2006). This provides indirect evidence that budesonide/formoterol delivered via MDI or Turbohaler may be therapeutically equivalent when used acutely for relief of asthma symptoms.

Table 1.8: Short-term bronchodilator comparison studies of formoterol via DPI and MDI

Study	Comparators	Dosing regimen	Trial design	Outcome
Corren 2007	B/F MDI 100/6µg F DPI 6µg	2 actuations 2 actuations	RCT, DB	Mean increase in 12-hour FEV_1 was 0.41L in B/F group and 0.44L in F group (NS)
Kaiser 2008	B/F MDI 200/6µg F DPI 6µg	2 actuations 2 actuations	RCT, DB	57% of patients in both groups had a ≥15% increase in FEV_1 within 60 min (NS); median time to ≥15% increase in FEV_1 was 10min in B/F group and 8min in F group (NS)
Miller 2008	B/F MDI 100/6µg F DPI 6µg	1, 2, 4 actuations 1, 2, 4 actuations	RCT, crossover	No significant differences between same-dose formoterol treatments in average 12-hour FEV_1, maximum FEV_1, and FEV_1 at 12 hours
Noonan 2006	B/F MDI 200/6µg F DPI 6µg	2 actuations 2 actuations	RCT, DB	Mean increase in 12-hour FEV_1 was 0.37L in B/F group and 0.35L in F group (NS)

B/F: budesonide/formoterol; F: formoterol; MDI: metered dose inhaler; DPI: dry powder inhaler; DB: double blind; RCT: randomised controlled trial; NS: non statistically significant difference between groups; L: litres.

1.25 Thresholds of high beta-agonist use requiring medical review

1.25.1 SABA thresholds defined by self-management plans

Salbutamol is usually prescribed at a dose of one to two inhalations as-required (GlaxoSmithKline Limited, 2011). The New Zealand Asthma and Respiratory Foundation 2004 asthma self-management plan recommends that patients seek medical review when reliever use is every two to three hours (Holt, Masoli and Beasley, 2004) (i.e. eight to 24 actuations per 24-hours). The Asthma UK Personal Asthma Action Plan recommends medical review when reliever use is every four hours or more often (Asthma UK, 2011).

Based on these recommendations, more than 16 actuations of salbutamol per 24-hours may be considered as the threshold of SABA use that requires medical review.

1.25.2 Budesonide/formoterol thresholds defined by self-management plans

The Symbicort SMART asthma action plan recommends that medical review is required if more than 12 actuations of budesonide/formoterol per 24-hours are used in the setting of worsening asthma (National Asthma Council Australia, 2013).

If a patient is prescribed two actuations twice daily (four actuations total) of budesonide/formoterol as maintenance therapy, then the use of more than eight actuations in excess of the four maintenance doses per 24-hours (i.e. more than 12 actuations in total) is the threshold requiring medical review.

1.25.3 Beta-agonist thresholds used in clinical trials

In the TRUST trial of regular versus as-needed salbutamol, 1600µg per day of salbutamol (i.e. 16 actuations of salbutamol 100µg per actuation) was chosen as the dose of salbutamol for the regular treatment group (Dennis et al., 2000). A prior study investigating the safety of as-needed formoterol defined a maximum threshold of 12 actuations of formoterol (72µg) per day (Tattersfield et al., 2001). If four actuations per day (6µg per actuation) are taken as maintenance therapy, then this allows an additional eight doses to be taken for relief of symptoms.

Considered together, the ratio of reliever actuations per day requiring medical review can be interpreted as more than eight budesonide/formoterol actuations (for SMART) to more than 16 salbutamol actuations (for Standard therapy) (i.e. an actuation ratio of 1:2).

1.26 Short-term bronchodilator equivalence of salbutamol and formoterol

The short-term bronchodilator equivalence of salbutamol and formoterol varies according to the dosing regimen (single versus repeated dosing), medication formulation (Turbohaler versus MDI) and study setting (acute asthma versus stable asthma) (Hampel, Martin and Mezzanotte, 2008; Balanag et al., 2006; Rubinfeld et al., 2006; Ankerst et al., 2005; Boonsawat et al., 2003; Rosenborg et al., 2002; Seberova and Andersson, 2000). The key bronchodilator comparison studies are summarised in Table 1.9.

Table 1.9: Short-term bronchodilator comparison studies of salbutamol and formoterol

Study	Comparators	Dosing regimen	Formoterol to salbutamol actuation ratio*	Study setting	Trial design	Outcome: formoterol versus salbutamol
Ankerst 2005 †	F: 12µg S: 200µg	Single dose	2:2 (1:1)	Stable asthma	DB, P, RCT, crossover	8% *v* 9% mean increase in FEV_1 at 3 minutes (NS, no p value)
Balanag 2006 ‡	B/F: 800/24µg S: 800µg	2 doses	8:16 (1:2)	Acute asthma	DB, P, RCT	30% *v* 32% mean increase in FEV_1 at 90 minutes (p=0.66)
Boonsawat 2003	F: 24µg S: 800µg	3 doses	12:24 (1:2)	Acute asthma	DB, RCT	37% *v* 28% mean increase in FEV_1 at 75 minutes (p=0.18)
Hampel 2008 §	B/F: 200/12µg S: 200µg	Single dose	2:2 (1:1)	Stable asthma	DB, RCT, crossover	0.2L *v* 0.3L mean increase in FEV_1 at 3 minutes (NS)
Rosenborg 2002	F: 6, 24, 72µg S: 200,1800µg	Single dose	4:18 (1:4.5)	Stable asthma	DB, RCT, crossover	Comparable increase in FEV_1 at 30 minutes between 24µg F and 1800µg S (no p value)
Rubinfeld 2006	F: 24µg S: 800µg	2 doses	8:16 (1:2)	Acute asthma	DB, RCT	6.6% *v* 9.3% increase in FEV_1 % predicted at 45 minutes (p=0.24)
Seberova 2000	F: 6, 12µg S: 100, 200µg	Single dose	2:2 (1:1)	Stable asthma	DB, RCT, crossover	11.8% *v* 11.4% increase in FEV_1 at 3 minutes between 12µg F and 200µg S (NS, no p value)

*: actuation ratio calculated on the basis of 6µg formoterol per actuation and 100µg salbutamol per actuation; †: F via MDI; ‡: B/F via Turbohaler; §: B/F via MDI; F: formoterol; B/F: budesonide/formoterol; S: salbutamol; DB: double blind; P: placebo controlled; RCT: randomised controlled trial; NS: non-statistically significant difference between groups; *v*: versus; L: litre.

The multiple-dose comparison studies of budesonide/formoterol or formoterol and salbutamol in acute asthma (Balanag et al., 2006; Rubinfeld et al., 2006; Boonsawat et al., 2003) support a short-term bronchodilator equivalence of 6µg formoterol to 200µg salbutamol (a 1:2 actuation ratio respectively) (Table 1.9).

1.27 History of asthma mortality epidemics

The previous sections have reviewed the differences in the efficacy of formoterol and salbutamol. There are also potential differences in the risks associated with the use of these two drugs and these will now be considered.

Asthma mortality peaks occurred during the 1960s and 1970s and with both 'epidemics', the use of beta-agonists with high intrinsic activity have been implicated.

1.27.1 Isoprenaline forte in the 1960s

An increase in asthma mortality occurring in England and Wales was initially described in the 1960s (Speizer, Doll and Heaf, 1968). Subsequently, an increase in mortality rates were observed in persons aged five to 34 in at least six developed countries, including Australia and New Zealand (Crane, 1993). There were conflicting views as to the cause of the epidemic (Stolley and Schinnar, 1978; Inman and Adelstein, 1969), but its occurrence correlated with the introduction of a high-dose inhaled preparation of the beta-agonist isoprenaline (isoprenaline forte) in these countries (Stolley and Schinnar, 1978).

One suggested mechanism for an increased risk of death included direct cardio-toxicity due to therapy with a beta-agonist with high intrinsic activity for cardiac adrenoceptors (Stolley and Schinnar, 1978; O'Donnell and Wanstall, 1974). This risk may have been potentiated by the presence of tissue hypoxia (Collins et al., 1969). Another suggested mechanism for an increased risk of death was the potential for patients to delay in seeking medical care during worsening asthma (Fraser et al., 1971), due to the symptomatic relief provided by the high intrinsic activity of isoprenaline forte at pulmonary beta-2 adrenoceptors (O'Donnell and Wanstall, 1974).

1.27.2 Fenoterol in the 1970s

The second peak in mortality occurred in New Zealand in the mid-1970s (Beasley et al., 1990). A series of case-control studies implicated the recent introduction of a high-dose preparation of inhaled fenoterol (Grainger et al., 1991; Pearce et al., 1990; Crane et al., 1989), a beta-agonist with high intrinsic activity at beta-1 and beta-2 adrenoceptors (Giles, Williams and Finkel, 1973). This increase in mortality correlated with an increase in New Zealand sales of fenoterol and death rates reduced when the sales of fenoterol were restricted (Pearce and Hensley, 1998).

Studies in healthy volunteers and stable asthma patients demonstrated that fenoterol had greater maximal inotropic and chronotropic effects than salbutamol after multiple, repeat dosing, and caused a greater maximum hypokalaemic effect (Bremner et al., 1996; Windom et al., 1990b). A subsequent study in patients presenting to the ED with acute asthma and comparing cumulative doses of up to 16 actuations of fenoterol or salbutamol, confirmed the significantly greater effect of

fenoterol on serum potassium and cardiac parameters (Newhouse et al., 1996). In addition, regular use of fenoterol has been associated with worse asthma control compared to as-required use (Sears et al., 1990).

As previously, there were conflicting views regarding causality between fenoterol and asthma death (Beasley, 2006; Garrett et al., 1996).

Formoterol, like fenoterol and isoprenaline, has high intrinsic activity for cardiac adrenoceptors, whilst salbutamol has a lesser ability to activate cardiac adrenoceptors (Table 1.10) (Decker et al., 1982; Giles et al., 1973). Considering that formoterol shares this pharmacological property of high intrinsic activity with two beta-agonists implicated in epidemics of asthma mortality, it is important to review the mechanisms for adverse events that were suggested with the use of isoprenaline and fenoterol, and to consider their relevance to the use of budesonide/formoterol with the SMART regimen (Cates et al., 2009; Johnston and Edwards, 2009; Hancox, 2006; Nelson, 2006; Tattersfield, 2006; Lipworth, 2001; Beasley et al., 1999; Tattersfield, 1994; Wong et al., 1990; Sears and Rea, 1987).

Table 1.10: Comparative pharmacology of beta-2 adrenoceptor agonists - safety

Beta-agonist	Intrinsic activity in the trachea *	Intrinsic activity in the atrium †
Isoprenaline	1.00	1.00
Fenoterol	1.07	0.89
Formoterol	0.94	0.94
Salbutamol	0.91	0.75

*: Ratio of the maximal response of each beta-agonist compared to the maximal response of isoprenaline, in guinea-pig trachea [value for isoprenaline is 1.0; higher values suggest greater intrinsic activity for pulmonary adrenoceptors].
†: Ratio of the maximal response of each beta-agonist compared to the maximal response of isoprenaline, in guinea-pig atria [value for isoprenaline is 1.0; higher values suggest greater intrinsic activity for cardiac adrenoceptors].

[Summarised and adapted from Decker et al. (1982) and Giles et al. (1973)].

1.28 Potential mechanisms for adverse effects with the use of formoterol

1.28.1 Direct drug toxicity in the setting of beta-agonist overuse

Formoterol's higher intrinsic activity at cardiac adrenoceptors may increase its potential to cause cardiac adverse effects such as tachycardia and myocardial rhythm disturbances when compared to salbutamol, particularly in the setting of beta-agonist overuse. In addition, this risk may be potentiated by the presence of myocardial hypoxia, if this occurred during a severe or life-threatening asthma attack.

As previously discussed, due to its higher intrinsic activity at the beta-2 adrenoceptor, formoterol may also have a greater potential for hypokalaemia, which may contribute to an increased risk of cardiac arrhythmias.

1.28.2 Delay in seeking medical help in the setting of worsening asthma

The greater maximal bronchodilatory effect of formoterol, coupled with its prolonged duration of action, may result in greater delays in seeking medical help for patients using the SMART regimen during worsening asthma compared to a Standard fixed maintenance dose regimen with salbutamol for relief. Delay in seeking medical help might also increase the risk of development of hypoxia prior to medical review and further exacerbate any direct toxic effects.

1.28.3 Tolerance to treatment

Tolerance to the bronchodilator effects of formoterol may result in a reduced response to the effects of budesonide/formoterol when used for relief of symptoms during worsening asthma. Alternatively, tolerance may reduce the protection that budesonide/formoterol provides against bronchoconstrictor stimuli. Tolerance will be discussed in further detail in section 1.30.

1.28.4 Beta-agonist overuse as an indirect marker of risk of life threatening asthma

A number of studies have demonstrated that beta-agonist overuse is a marker of risk of death (Abramson et al., 2001; Suissa, Blais and Ernst, 1994; Suissa et al., 1994; Spitzer et al., 1992). Beta-agonist overuse is also a marker of intensive care admission for asthma (Eisner et al., 2001) and ED visit or hospitalisation for asthma (Schatz et al., 2005).

1.29 Evidence for direct toxicity with high-dose formoterol use

There are dose-dependent adverse effects on cardiovascular and biochemical parameters following cumulative dosing with formoterol in asthma patients (Burgess et al., 1998). Thus, 16 actuations (6µg per actuation) produced significantly greater maximal increases in QTc and reductions in serum potassium, than doses of two, four or eight actuations, and for a greater duration of time (Burgess et al., 1998). Compared to treatment with two doses, 16 doses of formoterol increased QTc by

23ms and reduced serum potassium by 0.4mmol/L (Burgess et al., 1998), suggesting a clinically relevant effect. Increases in cardiac contractility, which is a measure of myocardial oxygen demand, were also significantly greater after 16 actuations compared with two actuations (Burgess et al., 1998).

In a study in healthy volunteers, the maximal increases in heart rate, QTc and cardiac contractility were similar following cumulative dosing with 20 actuations of formoterol (6µg per actuation) or salbutamol (100µg per actuation) (Bremner et al., 1993). However, the increases in cardiac contractility and heart rate persisted for a longer duration of time in formoterol-treated patients (Bremner et al., 1993). In addition, the maximal decreases in serum potassium, as well as the duration of this reduction, were greater following treatment with formoterol than salbutamol (Bremner et al., 1993). Thus, patients using high doses of budesonide/formoterol with the SMART regimen may have a greater 'at-risk' period of physiological disturbance.

Conversely, short-term studies testing lower doses of formoterol have demonstrated conflicting results regarding the risk of drug toxicity. One study used eight actuations of formoterol (6µg per actuation) (Rubinfeld et al., 2006) and another study used four actuations of budesonide/formoterol (400/12µg per actuation) (Balanag et al., 2006) for the treatment of acute asthma in the ED, in patients without significant concomitant disease. Comparator groups were treated with 16 actuations (100µg per actuation) of salbutamol in both trials (Balanag et al., 2006; Rubinfeld et al., 2006). Changes in serum potassium and QTc were not significantly different between formoterol and salbutamol-treated patients. However, in another study of

cumulative dosing with 12 actuations (6µg per actuation) of formoterol in acute asthma, minimum serum potassium was significantly lower in formoterol-treated patients compared to patients receiving 24 actuations (100µg per actuation) of salbutamol (Boonsawat et al., 2003).

Clinical adverse events following treatment with formoterol have also been reported in certain studies. Angina considered to be related to the study medication was reported in one patient who had received six formoterol actuations (Ind et al., 2002), whilst atrial fibrillation (AF) was reported in another study in which a patient received 12 daily doses of formoterol (72µg per day) for three consecutive days (Totterman et al., 1998).

It is important to recognise that the studies described above were generally undertaken in carefully selected patients under strictly controlled conditions and that maximum dose was limited. In a real-world setting with patients who have co-morbid conditions and who may self-administer beta-agonist doses in excess of those tested above during worsening asthma (Windom et al., 1990a), these short-term studies have demonstrated that there remains the potential for risk of direct adverse effects with the SMART regimen.

1.30 Tolerance

The effects of pulmonary tolerance may manifest in a number of ways (Tattersfield, 1993). In addition, the use of concomitant ICS does not necessarily protect against the development of these effects (Anderson, 2000; Taylor and Hancox, 2000).

1.30.1 Reduction in bronchodilator effect after regular formoterol treatment

A significant attenuation in the bronchodilator response to single (Yates et al., 1995) and cumulative (Newnham et al., 1995) dosing with formoterol has been demonstrated in short-term studies in which patients were treated with regular formoterol or placebo. In a six-month study in which patients received 24µg per day of formoterol, the bronchodilator response 30 minutes following formoterol dosing was initially reduced, before remaining stable for the remaining study period (FitzGerald et al., 1999). In the FACET study, the addition of formoterol to budesonide resulted in an immediate increase in morning PEFR, followed by a gradual decrease in the following 14 days, before reaching a steady-state level (Pauwels et al., 1997).

These studies demonstrate that tolerance to the bronchodilator effect of formoterol may occur after repeated dosing. In theory, this may reduce the effectiveness of extra actuations of budesonide/formoterol when taken for relief of symptoms for patients on the SMART regimen.

1.30.2 Reduction in response to SABA following regular formoterol treatment

There is evidence to suggest that whilst patients are on treatment with regular formoterol, there is significant tolerance to the bronchodilator effects of salbutamol in the presence of acute bronchoconstriction (Haney and Hancox, 2005a; Haney and Hancox, 2005b; Jones et al., 2001). This finding is important, as the response to rescue SABA therapy in the setting of acute asthma may be reduced (Haney and Hancox, 2007; Haney and Hancox, 2006). If adherence to maintenance budesonide/formoterol therapy is increased by use of the SMART regimen, then tolerance may pose a greater risk for patients on this regimen, particularly in the setting of worsening asthma requiring rescue SABA use, as might occur in the ED.

1.30.3 Reduced protection following bronchoconstrictor challenge

Loss of protection to the bronchoconstrictor challenges of AMP (Aziz et al., 1998b) and methacholine (Lipworth et al., 1998; Yates et al., 1995) have been demonstrated in patients receiving formoterol for one to two weeks. This effect was also noted after three months of treatment with formoterol but was not progressive (FitzGerald et al., 1999).

1.30.4 Rebound increase in bronchial reactivity after cessation of formoterol treatment

Following cessation of regular formoterol treatment, PC_{20} values for methacholine-induced bronchoconstriction remained above baseline values (FitzGerald et al., 1999; Yates et al., 1995), suggesting that a rebound increase in bronchial hyper-responsiveness may not occur once formoterol therapy is stopped.

1.30.5 Masking of worsening asthma

Concerns have been raised that LABA therapy may mask underlying deteriorating airway inflammation, particularly if patients are exposed to LABA monotherapy (Morales et al., 2012; Rodrigo and Castro-Rodriguez, 2012). This was the suggested mechanism in a patient who developed severe asthma after stopping ICS therapy but continuing with formoterol monotherapy (Arvidsson et al., 1991). This risk should theoretically be diminished by the use of combination ICS/LABA inhaler therapy (Beasley, Fingleton and Weatherall, 2013).

1.31 Tolerance to the extra-pulmonary effects of formoterol

Following regular treatment with formoterol, tolerance to the systemic effects of subsequent cumulative dosing has been demonstrated. Thus, the hypokalaemic and cardiac effects of repeated high dosing with formoterol, such as may occur during worsening asthma with the SMART regimen, are diminished if the patient is taking regular formoterol (van den Berg et al., 1998; Newnham et al., 1995). This may provide some protection from direct drug toxicity, though there is some evidence to suggest that use of concomitant ICS re-sensitises cardiac beta-2 adrenoceptors and may diminish the protective effect that extra-pulmonary tolerance may provide (Jackson and Lipworth, 2004; Aziz, McFarlane and Lipworth, 1998a).

1.32 Polymorphisms in the beta-2 adrenoceptor gene and the risk of adverse outcomes with formoterol treatment

In recent years, the beta-2 adrenoceptor gene (ADRB2) has been sequenced and polymorphisms occurring at amino acid position 16 (Gly16Arg) may be considered a 'risk factor' for adverse outcomes with LABA therapy in asthma (Kazani, Wechsler and Israel, 2010). Alterations in the amino acid composition of the beta-2 adrenoceptor from glycine to arginine at this position may alter the function of the receptor in response to binding with formoterol, and therefore predispose to a diminished clinical response (Szefler et al., 2012; Kazani et al., 2010).

In patients receiving either the SMART regimen or a fixed-dose budesonide/formoterol regimen with SABA for relief, the occurrence of severe asthma exacerbations were not affected by Gly16Arg genotype (Bleecker et al., 2007). In addition, Gly16Arg genotype did not predict the response to either therapy in terms of improvements in lung function or symptom scores (Bleecker et al., 2007). These findings suggest that genetic polymorphisms are unlikely to be the sole determinants of adverse outcomes associated with LABA therapy. Further studies are required to examine the impact of ADRB2 genotype on response to asthma therapy (Lipworth et al., 2013; Sayers, 2013).

1.33 Safety in long-term clinical trials with formoterol

No differences in the occurrence or patterns of AEs or SAEs were noted between the formoterol and terbutaline-treated groups in the first large-scale study of the use of formoterol as a reliever therapy (Tattersfield et al., 2001). However, patients with high baseline reliever use (greater than 12 inhalations per day of rescue medication during run-in) and patients with serum potassium values outside the reference range were excluded from study entry. In addition, patients who experienced more than one severe exacerbation in the study were withdrawn.

A previous analysis suggested a dose-response relationship for an increased risk of serious asthma events (including life-threatening asthma) with 48µg of formoterol per day compared to 24µg per day (Mann et al., 2003). Though this finding was not replicated in a subsequent prospective safety study (Wolfe et al., 2006), one patient in this study had a myocardial infarction considered to be related to formoterol treatment (24µg per day) and over 1% of patients on formoterol suffered from 'cardiac disorders' (Wolfe et al., 2006).

RELIEF (Pauwels et al., 2003b) was a safety and efficacy study of the use of formoterol as a reliever treatment compared to the use of salbutamol. There were no significant differences in the proportions of patients with AEs, cardiovascular-related AEs, SAEs or deaths between groups and there was a significant reduction in the number of asthma-related AEs in the formoterol-treated group. There were no restrictions on study entry based on baseline reliever medication use, though patients

who were enrolled were asked to contact study investigators if they used greater than 12 inhalations per day.

Clinically relevant adverse events have been reported in the individual primary SMART studies. O'Byrne et al. (2005) reported that there were study discontinuations due to cardiovascular adverse events and one patient suffered from AF thought to be related to SMART therapy in another study (Scicchitano et al., 2004). One SAE related to treatment with the SMART regimen was reported in another study, though there were no further details in the manuscript (Vogelmeier et al., 2005).

Considered together, these findings indicate that clinically significant adverse events associated with the use of formoterol as a reliever therapy may occur in the setting of controlled clinical trials.

1.34 Systematic reviews and meta-analyses of treatment with salmeterol in asthma

When examining the risk of occurrence of rare events, such as asthma-related death or cardiac-related death, meta-analyses of trials may help to assess the risk of these events (Weatherall et al., 2010a).

The importance of concurrent ICS therapy in reducing the risk of mortality when LABAs are used in asthma was demonstrated by a systematic review and meta-analysis of regular treatment with salmeterol (Table 1.11) (Weatherall et al., 2010b).

In this meta-analysis, regular treatment with salmeterol monotherapy, whereby concomitant ICS therapy was not mandated, significantly increased the risk of asthma-related death compared to treatment with placebo (Table 1.11). When the analysis was performed in trials in which salmeterol was used with ICS at baseline, the risk of asthma mortality was reduced. When the analysis was restricted further to trials in which patients received salmeterol and ICS in a single combination inhaler, there were no reported asthma deaths (Weatherall et al., 2010b).

Table 1.11: Risk of asthma death from a meta-analysis of randomised controlled trials of salmeterol use in asthma

Comparator	Odds ratio (95% CI) for asthma death
Salmeterol monotherapy versus placebo	7.3 (1.8 to 29.4)
Salmeterol with ICS versus ICS	2.1 (0.6 to 7.9)
Salmeterol/fluticasone in a combination inhaler versus ICS	0 deaths in 22,600 patients

These findings support the guidance against using LABA monotherapy in asthma patients (SIGN/BTS, 2012) and suggest that the concomitant use of ICS and salmeterol, particularly in the form of a combination ICS/LABA inhaler, is not associated with an increased risk of death.

1.35 Systematic reviews and meta-analyses of treatment with formoterol in asthma

Recent systematic reviews and meta-analyses have attempted to determine if there is an increased risk of asthma-related death with formoterol versus non-LABA therapy or, if this risk persists when formoterol is administered in combination with ICS,

compared to ICS alone. This second question is more clinically relevant in view of current recommendations that LABAs should always be co-prescribed with ICS (SIGN/BTS, 2012). A summary of meta-analyses of RCTs investigating these two questions are presented in Table 1.12 and Table 1.13 (Nelson et al., 2010; Beasley et al., 2009b; Cates et al., 2009; Sears et al., 2009; Wijesinghe et al., 2009; Cates, Cates and Lasserson, 2008; Levenson, 2008).

In all of the meta-analyses of mortality risk with formoterol, there has been insufficient power to determine a statistically significant difference between groups, due to the low overall rates of death or asthma-related deaths in the groups. These studies have suggested a non-significant 1.5 to 4.5-fold increased risk of asthma-related mortality in patients treated with formoterol compared to non-LABA treated patients across four analyses (Table 1.12) (Beasley et al., 2009b; Sears et al., 2009; Wijesinghe et al., 2009; Cates et al., 2008). Importantly, the risk of asthma-related mortality is non-significantly increased to between 2.32 and 7.34 in patients on concomitant formoterol and ICS versus ICS alone (Table 1.13) (Beasley et al., 2009b; Cates et al., 2009; Sears et al., 2009).

This finding is in contrast to the meta-analysis of trials in which patients were treated with salmeterol discussed previously (Weatherall et al., 2010b) and suggests that concomitant ICS and formoterol prescription may not protect against the risk of asthma-related mortality.

Table 1.12: Summary of meta-analyses of RCTs comparing formoterol versus non-LABA treatment in asthma - safety

Study	All cause mortality	Asthma-related mortality	Composite asthma endpoint †
Cates 2008*	OR (95% CI) 4.50 (0.41 to 49.49), NS	OR (95% CI) 4.54 (0.07 to 285.25), NS	-
Levenson 2008 [Formoterol]	RD (95% CI) -0.38 (-1.12 to 0.36), NS	No deaths	RD (95% CI) 3.80 (-1.8 to 9.40), NS
Levenson 2008 [Symbicort]	No deaths	No deaths	RD (95% CI) 7.49 (-1.47 to 16.44), NS
Sears 2009	RR (95% CI) 0.95 (0.50 to 1.92), NS	RR (95% CI) 1.57(0.31 to 15.1), NS	-
Beasley 2009	-	RR (95% CI) 2.53 (0.45 to 26), NS	-
Wijesinghe 2009	OR (95% CI) 1.1 (0.6 to 2.2), NS	OR (95% CI) 2.7 (0.5 to 26.7), NS	-
Nelson 2010	RR (95% CI) 0.64 (0.14 to 2.92), NS	No deaths	-

Comparisons are for formoterol versus non-LABA treatments (non-LABA treatments could include ICS, SABA or placebo); *: formoterol versus placebo; †: composite of asthma death, asthma intubation and asthma hospitalisation; NS: non-statistically significant; RR: relative risk; OR: odds ratio; RD: risk difference.

Table 1.13: Summary of meta-analyses of RCTs comparing formoterol with ICS versus ICS treatment in asthma - safety

Study	All cause mortality	Asthma-related mortality
Cates 2009	OR (95% CI) 5.83 (0.78 to 43.77), NS	OR (95% CI) 7.34 (0.15 to 369.72), NS
Sears 2009	RR (95% CI) 1.14 (0.53 to 2.73), NS	RR (95% CI) 2.32 (0.30 to 105), NS
Beasley 2009	-	RR (95% CI) 3.67 (0.41 to 174), NS

Comparisons are for formoterol with ICS versus ICS; NS: non-statistically significant;
RR: relative risk; OR: odds ratio.

A summary of the safety meta-analyses of RCTs of the SMART regimen are shown in Table 1.14 (Cates and Lasserson, 2009; Sears and Radner, 2009). The meta-analysis of the double-blind SMART clinical trial programme had insufficient power to rule out an effect on asthma mortality (Sears and Radner, 2009) (Table 1.14).

1.36 Implications of the formoterol meta-analyses and risk of asthma-related mortality

The above meta-analyses may be interpreted in a variety of ways but one possible explanation may be that current studies are insufficiently powered to detect a mortality risk with formoterol treatment (Beasley et al., 2009a). These studies (Sears and Radner, 2009; Wijesinghe et al., 2009), which were based on data from controlled clinical trials, may also underestimate the actual risk of asthma death that occurs in the clinical setting (Wijesinghe et al., 2009). This is because the risk of treatment with formoterol may be greater in real-world asthma patients compared to participants in carefully controlled clinical trials (Wijesinghe et al., 2009). With this in mind, there remains the possibility that asthma-related mortality may be increased by the use of formoterol and that this risk is not abolished by concomitant ICS use. One possible explanation for this may relate to formoterol's high intrinsic activity, which could predispose to an increased risk of adverse effects, particularly in patients using high doses for relief of symptoms.

Table 1.14: Meta-analyses of the SMART clinical trial programme in adults - fatal events

Study	Comparator	All-cause mortality, SMART *v* comparator RR/OR (95% CI)	Asthma-related mortality, SMART *v* comparator RR/OR (95% CI)
Cates 2009	Same fixed-dose ICS/LABA+SABA	0.34 (0.05 to 2.14)	0.33 (0.01 to 8.13)
Sears 2009	All double-blind RCTs	0.70 (0.21 to 2.30)	0.25 versus 0.16 *
Sears 2009	Open-label RCTs	1.38 versus 1.72 *	0 versus 0 *

*: This is a rate per 1000 treatment years (SMART versus comparators) with no statistical comparisons reported; RR: relative risk; OR: odds ratio.

1.37 Current concerns regarding the use of LABAs

Based on concerns regarding the potential increased risk of asthma-related death with LABAs including budesonide/formoterol (Kramer, 2009; Levenson, 2008), the Federal Drug Administration have imposed a 'black-box' restriction on the prescription of these drugs in the United States (Chowdhury and Dal Pan, 2010). There are conflicting viewpoints regarding the safety of LABAs in asthma (Rodrigo and Castro-Rodriguez, 2012; Sears, 2013; Drazen and O'Byrne, 2009) but large-scale clinical trials are now underway to assess the risk posed by the prescription of ICS/LABA therapy (Chowdhury, Seymour and Levenson, 2011).

1.38 Measurement of use of inhaled asthma therapy

The following sections will now review the possible methods to measure the use of inhaled asthma therapy.

The traditional method to measure adherence to inhaled asthma treatments is by patient self-report (for example, in response to a questionnaire) (Janson et al., 2008; Krishnan et al., 2004; Bender et al., 2000), or a daily diary of medication use (Rabe et al., 2006a; O'Byrne et al., 2005; Ind et al., 2002; van der Molen et al., 1997). Alternatives include measuring medication canister weight before and after patient use (Tashkin et al., 1991), prescription refill records from pharmacies and/or primary care clinics (Salamzadeh et al., 2005; Williams et al., 2004), drug level monitoring (Horn, Clark and Cochrane, 1990; Horn et al., 1989), physician estimate of medication use (Braunstein, Trinquet and Harper, 1996) and electronic monitoring of medication use (Yeung et al., 1994; Gong et al., 1988).

The utility of each of these methods has been reviewed (Cochrane, 2000; Cochrane, Horne and Chanez, 1999; Bender, Milgrom and Rand, 1997) and is summarised in Table 1.15 and Table 1.16. Use of canister weight, refill records, drug level monitoring, self-report and physician estimate do not provide data on actual day-to-day use of medication. Daily diaries and electronic monitors of medication use can provide data on patterns of use and are discussed further.

Table 1.15: Comparison of methods to measure use of inhaled asthma therapy (A)

Method	Description	Advantages	Limitations
Self-report	Patient answers a questionnaire relating to medication use, generally for a pre-defined period of use (e.g. 24 hours or one week)	• Simple to administer • Minimal resources required to collect data • Quick and cheap to undertake	• Accuracy limited by recall bias • Response may be affected by the patient reporting what they perceive their clinician wishes to see • Of limited use in collecting data on patterns of medication use
Daily diary	Patient completes a daily diary of medication use; diary may be in an electronic format (e.g. Personal Digital Assistant)	• Can provide data on medication use over a prolonged period of time • Data on symptoms and lung function may be collected simultaneously	• Requires the patient to remember to complete the diary on a daily basis • Risk of missing data due to non-completion by patient • Of limited use in collecting data on patterns of medication use
Canister weight	Medication canisters weighed before and after MDI use by the patient; change in weight is a measure of medication use	• Objective measurement of total number of doses used • Cheap to perform • Minimal additional resources required to collect data	• Does not provide data on patterns of medication use • Labour intensive
Prescription refill	Pharmacy and/or primary care clinic records analysed for prescription refills for medication	• Useful in collecting data on adherence to therapy over months/years • Cheap to undertake	• Does not provide data on patterns of medication use • Requires access to external databases (e.g. pharmacy)

Table 1.16: Comparison of methods to measure use of inhaled asthma therapy (B)

Method	Description	Advantages	Limitations
Drug level monitoring	Direct measurement of drug level in blood and/or urine	• Provides a quantifiable value which may be tracked with follow-up • May help to confirm treatment use	• Requires repeated blood and/or urine samples, making this impractical for use with most patients • Access to specialist laboratory testing required, which is not routinely available • Does not provide data on patterns of medication use
Physician estimate	Estimate of medication use based on physician's perception	• Quick and requires no additional resource	• Inaccurate and unreliable
Electronic monitor	Electronic monitor records inhaler actuation (to the nearest second); data can be downloaded at intervals	• Can provide accurate data on actual patterns of medication use • May be used to record treatment use over a prolonged period e.g. weeks/months • Does not require a change in patient behaviour	• Data accuracy may be affected if an invalidated and/or unreliable monitor is used • May not record medication inhalation • Expensive and may require additional quality control processes

1.38.1 Daily diary versus electronic monitoring

Daily diaries can be used by patients to record medication use. They have, however, been shown to be unreliable methods to quantify medication usage when compared to electronic monitoring (Milgrom et al., 1996; Rand and Wise, 1994; Spector et al., 1986). Use of treatment is generally over-reported with this method, possibly because patients document what they perceive their clinician wishes to see. In addition, daily dairy use over a six-month study period may be impractical and may be limited by non-completion and subsequent missing data. Requiring patients to complete a daily dairy, even if provided in an electronic format such as a Personal Digital Assistant, requires a change from usual behaviour and may affect the generalisability of data collected by this method. Use of daily diaries is therefore recognised to be a poor guide to actual use of medication. Electronic monitors have the advantage of being objective (Cochrane et al., 2000) and provide accurate data on patterns of actual medication use (Perrin et al., 2010). A recent critical appraisal has highlighted the need for electronic monitoring to obtain objective data on the actual use of treatment by patients on the SMART regimen (Chapman et al., 2010).

1.38.2 Electronic monitoring of medication use

Several electronic monitors have been developed over the past 30 years, for use with both MDIs and DPIs (Ingerski et al., 2011; Denyer, 2010). The first such monitor was the Nebulizer Chronolog, which attached to and recorded actuations from MDIs (Coutts, Gibson and Paton, 1992; Gong et al., 1988; Spector et al., 1986). Other monitors have been developed, including the Doser CT, MDI Log, SmartMist and the SmartTrack (Foster et al., 2012b; Weinstein, 2005; Julius, Sherman and

Hendeles, 2002; Rand et al., 1992). Several of these monitors continue to be available for use in clinical trials (Foster et al., 2012b; Spaulding et al., 2012; Apter et al., 2011; Rand et al., 2007). Each device has its own strengths and limitations and Table 1.17 is a summary of their key features.

The Turbuhaler Inhalation Computer, an electronic monitor for use with Turbohaler DPIs, was developed for use in the 1990s, but was found to be highly unreliable (Bosley, Parry and Cochrane, 1994). The monitor contained a microphone, which recorded the 'click' heard when the inhaler was loaded by a patient, as well as the noise associated with inhalation, and used this to record that a dose had been taken. 76/215 (35.3%) of monitors malfunctioned in the trial, with resulting impact on data interpretation (Bosley, Parry and Cochrane, 1994).

At the time of PhD commencement in 2010, validated and reliable monitors for use with the Symbicort Turbohaler (budesonide/formoterol DPI) were not available.

Table 1.17: Key features of electronic monitoring devices

Monitor	Function	Features	Accuracy	Disadvantages
Smartinhaler Tracker (Nexus6, NZ)	Plastic casing into which the MDI medication canister is inserted	• Records date and time stamp to the nearest second • Data downloadable • Can be re-used • Stores up to 3200 logs	98-99%	• Medication canister needs to be securely inserted for accurate recording • Vulnerable to moisture • Inhalation not recorded
SmartTrack (Nexus6, NZ)	Plastic casing which fits around a standard MDI canister and sleeve	• Records date and time stamp to the nearest second • Rechargeable battery • Monitor is transferable	97-99%	• Not available at the time of PhD commencement • Initial validation study published in 2012; further data on reliability required
Doser CT (MediTrack Products, USA)	Plastic sleeve that is placed on top of a MDI canister. Pressure-actuated sensor records MDI canister depression	• LCD counters display total actuations remaining and total number of actuations per day • Records data for 45 days • Transferable	94%	• No date or time record; records number of actuations only • Unable to download data to a computer • Inhalation not recorded
MDI Log (Life Link Monitoring, USA)	Monitor which is permanently attached to the MDI and records actuation and inhalation	• Records date and time of actuation • Records inhalation • Data downloadable	90%	• MDI must be sent to manufacturer for installation of the monitor • Monitor is not transferable between inhalers
SmartMist (Aradigm Corp, USA)	Device which encloses the entire inhaler except the mouthpiece	• Records time and date • Gives technique error feedback • Data downloadable	100%	• Significantly alters the appearance of the inhaler • May be considered too large/inconvenient by some patients

1.38.3 Covert electronic monitoring of inhaler use

There is a potential ethical issue regarding the use of covert electronic monitoring, whereby participants are not informed that their inhaler use is being monitored, as this may breach the requirement to provide fully informed consent (Riekert and Rand, 2002; Rand and Sevick, 2000). Covert monitoring may however reduce the occurrence of bias due to a change in patient behaviour and medication usage patterns, which is a possible consequence of participant awareness of being monitored. Prior studies have used this approach, whereby participants are not aware of the detailed capabilities of the electronic monitors that they are using during the study (Tashkin et al., 1991; Gong et al., 1988; Spector et al., 1986). In clinical trials investigating patterns of medication use, which may subsequently help to provide information on the risks and benefits of treatments used in clinical practice, collection of data using covert monitoring is acceptable provided the risk to participants is minimal (Riekert and Rand, 2002; Rand and Sevick, 2000).

1.38.4 Accuracy of electronic monitors

The validity of an electronic monitor refers to the ability of the monitor to actually measure inhaler actuations as per its intended design. This can be achieved by comparing measurements recorded by the monitor with those from one of the other measures of medication use described above, or with another validated electronic monitor of alternative design. However, given the limitations with non-electronic measurement techniques and because electronic monitoring is likely to represent the 'gold standard' (i.e. the most accurate of the methods), demonstrating validity requires careful validation processes.

Validity can be established in a number of ways. Laboratory ('bench') testing under standardised conditions is the usual first step. Actuations recorded by the electronic monitor are compared to a diary log (Spector et al., 1986). The advantage of this approach is that information on monitor performance in a variety of domains can subsequently be used to inform clinical trial protocols. A disadvantage is that the monitors are not exposed to 'real-world' conditions.

'Field' testing involves testing of monitor accuracy in a small sample of patients over a short time-frame. This is generally undertaken after initial bench testing. Recordings made by the monitor may be compared to a daily dairy of medication use kept by the patient (Foster et al., 2012b). An advantage of this approach is that it may provide information on monitor performance when exposed to 'real-world' conditions during use by asthma patients. A disadvantage is that data interpretation may be limited by inaccuracies with the daily diary method. An alternative method to validate the total number of doses recorded by the monitor may be to compare with canister weight. This, however, does not provide information on validity in recording patterns of use of medication.

1.38.5 Dose dumping

Dose dumping is the term used to describe the observation that some participants, who are aware that the total number of inhaler doses used is being electronically measured, intentionally actuate their inhalers in quick succession, to simulate adherence to treatment and the trial protocol. As the electronic monitor is able to record actuation date/time in addition to the total number of doses over a study period, it is possible to identify days on which this pattern of use is observed.

This practice was first described in a trial where ipratropium or placebo MDI use was electronically monitored in a subset of COPD participants in the Lung Health Study (Rand et al., 1992). In this study, dose dumping was defined as ≥100 actuations within three hours. Using this definition, approximately 12-15% of their participants had at least one dose dumping episode over four months. The authors (Rand et al., 1992) observed that these episodes generally occurred either on the day of the scheduled study visit or in the preceding few days.

In a study of adherence to non-bronchodilator MDI asthma therapy using the Nebulizer Chronolog electronic monitor, 'multiple simultaneous actuations' (MSA) were defined as ≥10 actuations with the same time stamp (Mawhinney et al., 1991). 11/34 (32%) of participants were observed to have at least one day with MSA over three months. 37% of days with MSA occurred either on the day of, or the day preceding, a study visit. The authors suggested that this behaviour might have indicated an attempt to convince the investigators that trial processes and medication use were being adhered to. They also suggested that in trials using electronic monitoring, measures to limit the impact of dose dumping data on the analysis required further consideration.

A study investigating adherence to a maintenance combination anti-inflammatory/SABA MDI (nedocromil/salbutamol) used Nebulizer Chronologs to measure MDI use in 202 asthma patients (Braunstein et al., 1996). Dose dumping was observed on the day of the study visit. The removal of electronic actuation data on the day of the study visit was suggested as a measure to limit the impact of this erroneous data on the final analysis.

In a prior study of adherence to maintenance therapy using the Tracker electronic monitors, dose-dumping was defined as ≥10 actuations within three hours (Charles et al., 2007). This was observed on 53 occasions, with 12 episodes (23%) occurring on the day of the study visit.

In summary, it is of importance that trials utilising electronic monitoring of MDI use consider the impact that dose dumping may have on data collection and the final analysis. There is, however, no consensus definition for dose dumping which can be applied to clinical trials. Furthermore, high-dose use of inhaled therapy for actual therapeutic use, rather than dose dumping, might be observed in more severe asthma patients, in patients who are high reliever medication users and in trials where monitoring of both maintenance and reliever asthma treatments are performed. Consequently, it may be difficult to separate dose dumping from actual therapeutic use of the inhaler by implementing a specific threshold value as used in the trials above. An alternative approach is to remove electronic data on the day of study visits prior to the final analysis, as dose dumping may occur on these days.

1.39 Smartinhaler Tracker electronic monitors

The Smartinhaler Tracker (Nexus6 Limited, Auckland, New Zealand) is a battery-powered electronic monitor that records the date and time of MDI actuations. The monitor comprises of a plastic casing (the monitor), into which a conventional medication canister can be inserted. The monitor casing incorporates a battery, switch and electronics which record the number, date and time (to the nearest

second) of the depression of the canister during actuation. Thus, the monitor combined with a medication canister can be used to measure use of inhaled therapy delivered via an MDI.

A connection point is incorporated into the base of the casing, allowing the monitor to be connected via a USB cable to a computer. Using dedicated computer software, inhaler actuation data can be viewed, saved onto the computer or a compact disc (CD) or transferred to a website-based database via the internet.

The Trackers are manufactured of plastic with similar properties to the commercial MDI sleeves and with actuator designs which replicate those of their commercial counterparts, in order to effect comparable drug delivery. Drug output and particle size testing conducted by an independent laboratory have previously been undertaken for the Ventolin Tracker and equivalent drug delivery to the commercial counterpart has been demonstrated (Nexus6 Limited, 2011).

1.39.1 Bench validation studies

The monitor has been validated for use in two laboratory studies. The first study tested the accuracy of 10 Trackers over 30 days, simulating maintenance or 'low' reliever medication use (two actuations performed twice per day) (Burgess et al., 2006). Tracker performance in recording doses from salbutamol MDIs (100µg per dose – Ventolin) was assessed in this study (two of the 10 monitors). Tracker accuracy was compared with a diary log and with a previously validated electronic monitor of alternative design, the Doser CT. In addition, accuracy of the Trackers in recording rapidly-performed actuations (30 times in quick succession) was assessed.

Five of the Trackers were 100% accurate in recording maintenance/low reliever actuations, when compared to the diary or Doser CT. In the remaining five Trackers, either the first or both the first and second doses were not recorded, but the remainder of actuations were all recorded correctly. When the set-up process for the monitors was repeated so that all Trackers were actuated during the process of loading a medication canister, the subsequent doses were correctly recorded. All date/time logs were 100% accurate when compared to the diary. No erroneous additional actuations were recorded by any of the Trackers at any point. The Trackers recorded 30 actuations in rapid succession with 100% accuracy.

Thus, with correct initial setup of the monitor, which involves actuating the monitor during canister loading, this study established the validity of the Tracker monitors in recording the number, date and time of salbutamol MDI actuations in the bench setting.

The second study investigated the accuracy of Tracker monitors in measuring actuations of budesonide/formoterol MDIs (200/6µg per dose - Vannair) (Chan et al., 2009). Three monitors were tested over 48 hours, with both maintenance/low reliever dosing and 30 doses performed in rapid succession. Tracker accuracy was compared with a diary log. A spacer fit test was also undertaken.

Two of the three monitors were 100% accurate in recording maintenance/low reliever doses. One monitor recorded one extra actuation on two occasions during this period, most likely related to an incomplete depression of the canister during actuation. All rapid actuations were correctly recorded. Date/time logs were

recorded 100% accurately. The overall accuracy in recording actuations was 98% and good spacer fit was documented.

This study demonstrated the validity of the Tracker monitors in recording the number, date and time of budesonide/formoterol MDI actuations in the bench setting.

1.39.2 Smartinhaler Tracker use in clinical studies

The Smartinhaler Tracker has been utilised to measure adherence to therapy and patterns of medication use in clinical studies in both adults (Turton, Glasgow and Brannan, 2012; Perrin et al., 2010; Charles et al., 2007) and children (Klok et al., 2012; Burgess, Sly and Devadason, 2010; Burgess et al., 2008; Burgess et al., 2007).

Trackers with an audiovisual reminder function were used in a six-month RCT of fluticasone MDI involving 110 adults (Charles et al., 2007). This study established the feasibility of using covert electronic monitoring with the Tracker in a clinical trial setting. Participants were not told that their medication usage was being recorded, as this may have had the potential to change patient behaviour and therefore affect interpretation of the data collected. This approach received Ethics approval as it was unlikely to lead to patient harm and would improve the accuracy of the data obtained.

A six-month RCT involving 111 adults investigated adherence with single or combination ICS/LABA inhaler therapy, using Trackers to monitor treatment with fluticasone, salmeterol or fluticasone/salmeterol MDIs (Perrin et al., 2010). Monitors were downloaded out of sight of participants at study visits, in order to

preserve the practice of covert monitoring. The Trackers, whilst remaining patient-specific, were re-used by reloading with new medication canisters at study visits.

Turton et al. (2012) investigated the feasibility of using bronchial hyper-responsiveness as an aid to asthma management in 13 adults in primary care and used Trackers to measure ICS use by MDI. In two of these patients, device malfunction resulted in data loss (Turton et al., 2012).

In summary, the Tracker has been validated for use in laboratory studies and its utility in the clinical trial setting has been established in long-term studies.

1.40 Hypothesis

Inhaled corticosteroid/long-acting beta-agonist therapy delivered from a combination inhaler is the mainstay of treatment in patients with moderate to severe asthma (SIGN/BTS, 2012; GINA, 2011). It can be prescribed either in accordance with a 'Standard' fixed maintenance dose regimen together with a short-acting beta-agonist for relief of symptoms, or according to the 'SMART' (Single combination inhaler as Maintenance And Reliever Therapy) regimen, in which a combination budesonide/formoterol inhaler is used for both maintenance and as-needed reliever use. Randomised controlled trials show that in moderate to severe asthma, treatment with the SMART regimen leads to a reduction in severe asthma exacerbations when compared with the Standard regimen (Rabe et al., 2006a; O'Byrne et al., 2005). The generalisability of this finding is limited by the reduction in maintenance ICS dose which occurred at randomisation and the eligibility criteria for these studies which excluded patients who had high baseline use of their reliever medication. As there was no robust data on actual patterns of medication use, it is not possible to determine whether the reduction in severe exacerbations with the SMART regimen is due to more regular ICS exposure through as-needed reliever use in otherwise poorly adherent patients, or self-titrated budesonide/formoterol use during worsening asthma. Also, it is unknown if the SMART regimen leads to delays in seeking medical care in the setting of severe exacerbations, or whether it may result in a greater systemic corticosteroid load.

This thesis reports on the results of a randomised controlled trial of SMART versus Standard therapy in asthma patients at risk of severe exacerbations, using electronic monitoring to determine patterns of actual medication use. Use of electronic monitoring allowed beta-agonist overuse to be applied as a marker of risk of life-threatening asthma (Abramson et al., 2001; Eisner et al., 2001; Suissa, Blais and Ernst, 1994; Spitzer et al., 1992). The primary hypothesis was that treatment with the SMART regimen would lead to a reduction in the risk of high beta-agonist use. Secondary aims were to investigate whether patients treated with the SMART regimen were less likely to seek medical review in the setting of beta-agonist overuse and to determine whether any reduction in severe asthma exacerbations would be at a cost of a higher systemic corticosteroid burden.

1.41 Aims of this thesis

- To determine the accuracy of self-reported use of inhaled asthma therapy versus electronic monitoring of inhaler use, from a retrospective analysis of a previously undertaken RCT.
- To validate the long-term accuracy of the Tracker electronic monitors used in the principal RCT, during bench testing.
- To determine whether budesonide/formoterol when prescribed as per the SMART regimen will reduce the risk of high beta-agonist use compared to Standard therapy in real-world asthma patients with a recent exacerbation, using electronic monitoring to measure actual medication use. The rationale

for this aim was that prior studies using self-report to measure medication use have suggested that beta-agonist overuse is reduced by treatment with the SMART regimen compared to the same fixed-dose of budesonide/formoterol with SABA for relief (Rabe et al., 2006a; O'Byrne et al., 2005).

- To determine if the SMART regimen leads to an increased risk of high beta-agonist use without medical review. The rationale for this aim was that the greater intrinsic efficacy of formoterol together with its prolonged duration of bronchodilatory action, as compared to salbutamol, may result in greater delays in seeking medical assistance for patients using the SMART regimen during worsening asthma compared to use of the Standard regimen. Delay in seeking medical review during severe exacerbations of asthma may contribute to a fatal outcome (Fraser et al., 1971).
- To determine whether budesonide/formoterol used as per the SMART regimen reduces severe asthma exacerbations when compared to Standard therapy in at risk asthma patients.
- To determine if the SMART regimen increases the systemic corticosteroid burden compared to the Standard regimen. The rationale for this aim was that treatment with the SMART regimen may allow exposure to high doses of ICS and for a prolonged duration, which may contribute to an increased systemic corticosteroid burden.
- To report on the performance of the Tracker electronic monitors in the principal RCT, based on the use of pre-trial and within-trial quality control protocols.

Chapter Two: Accuracy of self-report versus electronic monitoring of MDI use

2.1 Introduction

Improving adherence to asthma therapy is a key priority to enhance asthma care (Holgate et al., 2008; National Heart, Lung, and Blood Institute, 2007; Horne, 2006). Identifying non-adherence to prescribed maintenance inhaled treatment, such as ICS or LABA, is therefore the first step in the process of improving patients' adherence to treatment (Heaney and Horne, 2012). In addition, assessment of the use of 'reliever' inhaled therapy, such SABAs, is a key element of monitoring current asthma control (SIGN/BTS, 2012; National Heart, Lung, and Blood Institute, 2007; Nathan et al., 2004; Juniper et al., 1999).

Patient self-report is the traditional method of measuring use of inhaled asthma therapy (Pauwels et al., 1997; Greening et al., 1994). Self-report is an easy, cheap and convenient method but has several significant limitations. Firstly, self-report relies on the patient's recollection of events, which may become inaccurate over time. Secondly, information obtained via self-report may be inaccurate, due to misrepresentation of use by the patient. Patients may therefore report what they perceive their physician wishes to hear, in an effort to appear adherent to prescribed maintenance treatment and/or not over-reliant on SABA treatment. Thirdly, self-report does not allow information to be collected on patterns of use of medication.

Electronic monitoring of inhaled asthma medication has been developed and validated as a reliable and accurate method to collect data on treatment adherence (Apter, Tor and Feldman, 2001; Simmons et al., 1998). Various comparisons of self-report versus electronic monitoring have been undertaken (Bender et al., 2000; Berg, Dunbar-Jacob and Rohay, 1998; Spector et al., 1986). These studies have demonstrated the superiority of electronic monitoring over self-report as a measure of medication use and have also shown that patients generally tend to overestimate their adherence to maintenance treatment. It is therefore important to recognise the limitations of self-report, particularly the potential discrepancy between what is reported and the actual use of treatments.

In a recently published 24-week, prospective RCT of adherence with single or combination ICS/LABA therapy in asthma, 111 patients were randomised to receive fluticasone and salmeterol twice daily, either as a combination ICS/LABA inhaler or as separate inhalers, to take in addition to their usual reliever therapy (Perrin et al., 2010). Adherence to treatment during the study period was measured using covert electronic monitoring of MDI actuation utilising Smartinhaler Tracker electronic monitors. Additionally, data on adherence to treatment in the one week prior to study visits were also collected by self-report questionnaire. This allowed a direct comparison between self-report and electronic monitoring for the week prior to study visits.

2.2 Hypothesis

The hypothesis was that self-report was not an accurate measure of actual use and that patients who under-used would over-report their use of maintenance inhaled therapy.

2.3 Aim

The primary aim of this analysis was to investigate the association between self-report and actual medication use as measured by electronic monitoring for single and combination ICS and LABA MDI therapy.

2.4 Methods

This was a retrospective analysis of a prospective RCT (Australian and New Zealand Clinical Trials Registration number ACTRN12606000508572) investigating treatment adherence with single and combination ICS and LABA therapy. Full details of the trial have previously been published (Perrin et al., 2010).

The RCT involved adults with stable asthma aged 16 to 65 who were randomised to receive one of the two following treatment regimens for a duration of 24 weeks: 125µg fluticasone and 25µg salmeterol in a combination inhaler, two actuations

twice daily (total four actuations per day); or, 125µg fluticasone and 25µg salmeterol in two separate inhalers, two actuations twice daily (total four actuations per day for each inhaler). Treatment adherence was monitored using Smartinhaler Tracker electronic monitors.

Participants were seen in the clinic on five occasions over the 24-week study period. Randomisation occurred at Visit 1 and Visits 2 to 5 were every six weeks thereafter. Participants were not informed that the electronic monitor could record MDI actuations and were not advised that adherence to treatment was the primary outcome for the study. At Visits 2 to 5, data from the monitors were downloaded to a computer, out of sight of participants. Monitors were cleaned, reloaded with new medication canisters and returned to participants. Participants were also asked to complete a self-report questionnaire on treatment use in the seven days prior to the clinic visit using the following wording: '*During the past week, it is estimated that you will have used 28 puffs of (each) of your study inhalers. How many puffs of your inhaler have you taken during the last week?'*

For this analysis, electronic monitoring data for the week prior to study Visits 2 to 5 were extracted for each participant. Doses that were identified as being dose dumping were removed from the analysis. As per the original study, dose dumping was defined as six or more actuations within a five-minute period. Self-report data that was incomplete or unanswered was also not included in the analysis. Comparison was made between self-reported medication use and actual use as measured by electronic monitoring at visits where both complete self-report data and electronic monitoring data were available.

2.4.1 Statistical methods

Measurement of agreement between the electronic monitor record of actuations and self-report at each visit used Bland-Altman plots with calculation of limits of agreement (Myles and Cui, 2007; Bland and Altman, 1999; Bland and Altman, 1986). Bland-Altman plots summarise agreement by relating the difference between two measurements to the average of two measurements, in this case electronic monitoring and self-report. The differences represent bias of one measurement with respect to the other and the variability in the differences are represented on a plot, together with limits of agreement defined as plus or minus two Standard Deviations (SD) of the differences.

In addition, mixed linear models examined the extent to which variability in electronic monitoring and self-report was due to variability between different patients or variability within patients. In these models, there are fixed effects for visit and whether the inhaler count was by electronic monitor versus self-report, as well as an interaction between these two effects to test if differences depended on the particular visit, and random effects for participants. Variance components and calculation of the intra-class correlation (ICC) coefficient from the analyses illustrate the proportion of variability due to the different participants and left-over variability representing variability within participants. ICC varies from zero to one and a value close to one is consistent with most of variability coming from different participants.

SAS version 9.2 was used.

2.5 Results

There were 111 participants randomised (54 participants allocated to the separate inhaler group and 57 participants to the combination inhaler group). The characteristics of the study participants are summarised in Table 2.1.

Table 2.1: Characteristics of trial participants

	Single inhalers group	Combination inhaler group
Age, years	49.2±11.2	45.4±13.8
FEV_1, Litres	2.51±0.81	2.60±0.75
FEV_1 % predicted	79.9±19.6	82.3±18.3
ACQ-7 score	1.3±0.7	1.2±0.7
Adherence (%) *	73.7±36.0 † / 76.7±30.5 ‡	82.4±24.5

Plus/minus values are mean ± SD. *: Adherence (defined as the number of doses taken as a percentage of those prescribed) in the final 6-week period of the study; †: fluticasone single inhaler; ‡: salmeterol single inhaler. FEV_1: Forced Expiratory Volume in 1 second (Litres). ACQ-7: Asthma Control Questionnaire-7.

There were 104 episodes of dose dumping which were not included in the analysis. Paired data from 198 of a potential 216 (91.7%) study visits for the separate inhaler group and 211 of a potential 228 (92.5%) study visits for the combination inhaler group were included in the analyses. Data from 35 visits were not included due to

incomplete self-report questionnaires (three visits), monitor malfunction, damage and non-return of the inhalers at study visits (19 visits), or participant withdrawal (13 visits).

2.5.1 Fluticasone separate inhaler

Across the four study visits, the mean ± SD of the average of electronic monitoring and self-report was between 22.6 ± 6.2 and 24.3 ± 8.3 actuations (Table 2.2). The mean ± SD of electronic monitoring use minus self-report was between -4.6 ± 10.1 and -8.4 ± 12.2 actuations (Table 2.2). Figure 2.1 (a-d) shows Bland-Altman plots for the four study visits. Limits of agreement for electronic monitoring and self-report were wide, ranging between 20.2 and 25.6 actuations. The percentage of participants whose self-reported use was the prescribed 28 puffs was between 62% and 69%. Participants who under-used fluticasone were more likely to over-report actual use, whilst those who over-used were more likely to under-report. The greater the degree of under-use, the greater the magnitude of over-report and the greater the degree of over-use, the greater the magnitude of under-report.

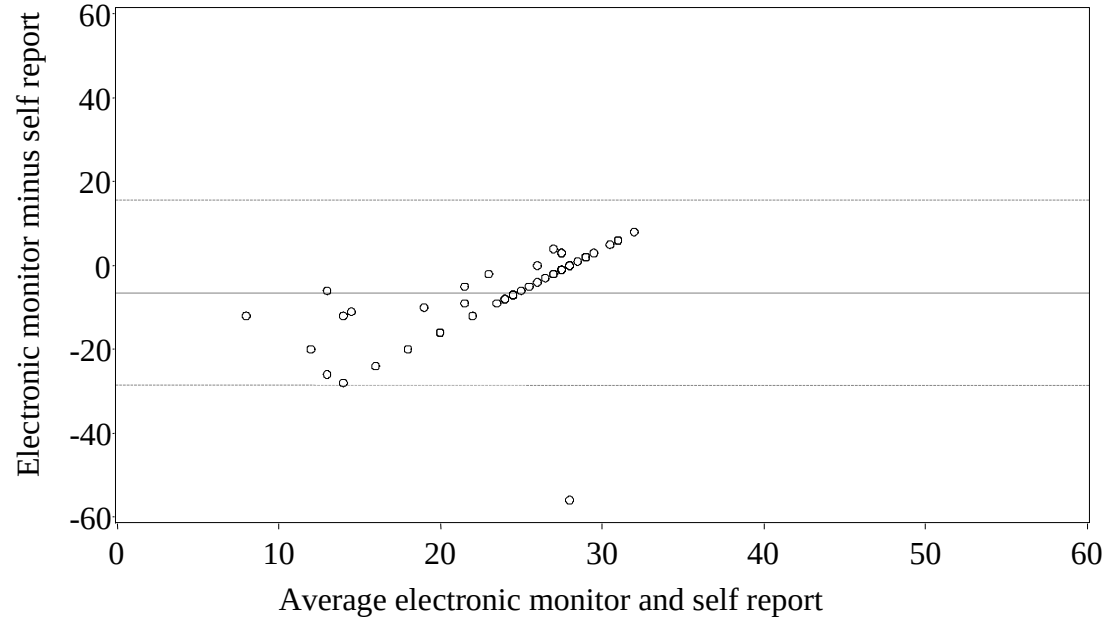
Table 2.2: Self-report and electronic monitoring for the fluticasone separate inhaler

Variable	Visit 2 *	Visit 3 †	Visit 4 ‡	Visit 5 §
Self-reported use of 28 puffs, number of participants (%)	34 (69.4)	32 (62.8)	33 (67.4)	31 (63.3)
Self-report, number of actuations	27.1±5.3	26.5±6.4	26.4±6.0	27.4±5.5
Electronic monitor, number of actuations	20.5±10.0	22.0±12.2	18.7±11.1	19.0±10.8
Electronic monitor minus self-report, number of actuations	-6.6±11.1	-4.6±10.1	-7.8±12.8	-8.4±12.2
Average electronic monitor and self-report, number of actuations	23.8±5.8	24.3±8.3	22.6±6.2	23.2±6.0
Limits of agreement, number of actuations	Plus/minus 22.2	Plus/minus 20.2	Plus/minus 25.6	Plus/minus 24.4

*: N=49; †: N=51; ‡: N=49; §: N= 49. Plus/minus values are mean ± SD.

Figure 2.1: Bland Altman plots for the difference between electronic monitor and self report, against the mean of electronic monitor and self report, for the fluticasone inhaler

a) Visit 2

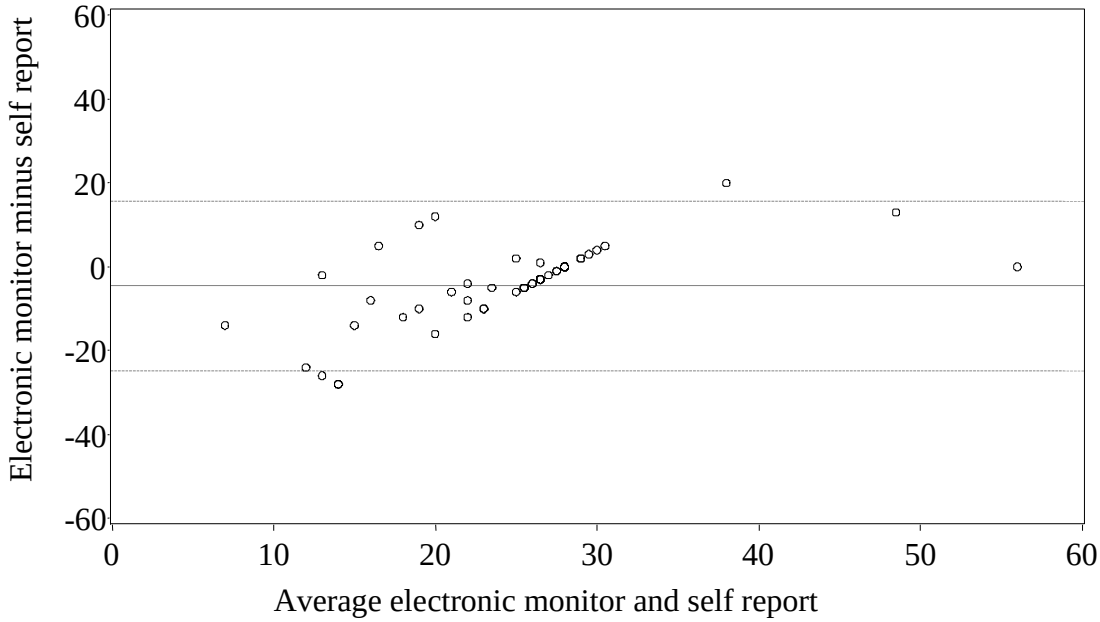


Numbers are actuations

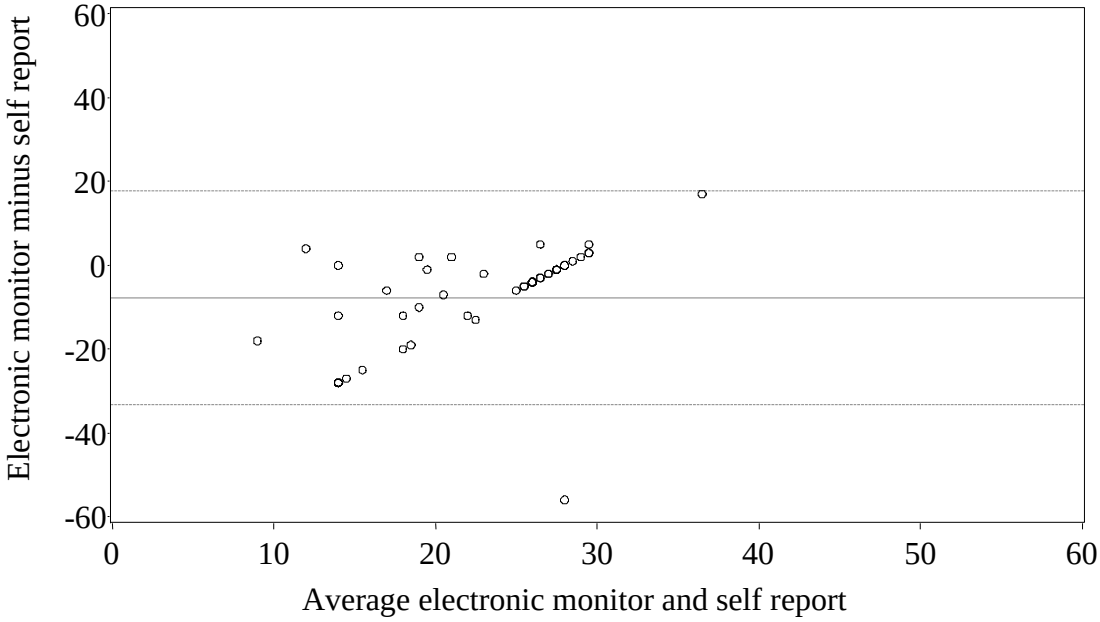
——— : Mean difference between electronic monitor and self-report

— — – : Limits of agreement (plus or minus 2 SD of the mean difference between electronic monitor and self-report)

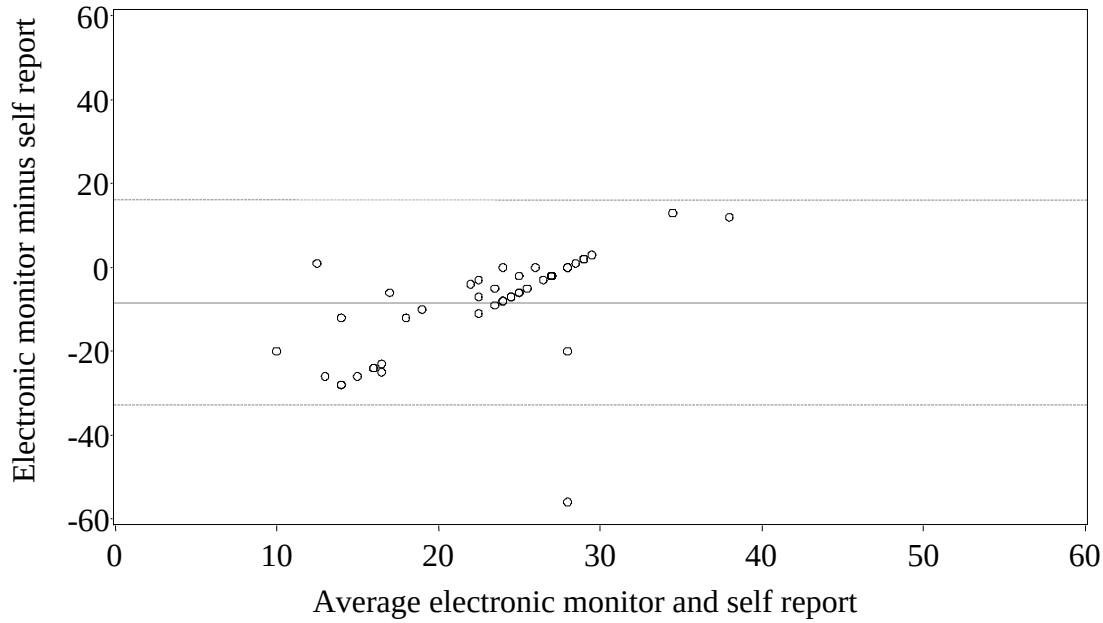
b) Visit 3



c) Visit 4



d) Visit 5



There was no evidence that the difference between electronic monitor and self-report was different at the different visits, p for interaction 0.37. The estimated difference for electronic monitoring minus self-report averaged over all visits was -6.8 actuations (95% CI -8.4 to -5.2). The variance components for patient variability was 10.36 and residual variability 67.5, ICC 0.13.

2.5.2 Salmeterol separate inhaler

Across the four study visits, the mean ± SD of the average of electronic monitoring and self-report was between 23.4 ± 6.5 and 23.8 ± 6.4 actuations (Table 2.3). The mean ± SD of electronic monitoring use minus self-report was between -3.9 ± 10.1 and -7.0 ± 11.1 actuations (Table 2.3). Figure 2.2 (a-d) shows Bland-Altman plots for the four study visits. Limits of agreement for electronic monitoring and self-report were wide, ranging between 16.8 and 22.2 actuations. The percentage of participants whose self-reported use was the prescribed 28 puffs was between 60% and 67%. Participants who under-used salmeterol were more likely to over-report actual use, whilst those who over-used were more likely to under-report. The greater the degree of under-use, the greater the magnitude of over-report and the greater the degree of over-use, the greater the magnitude of under-report.

There was no evidence that the difference between electronic monitor and self-report was different at the different visits, p for interaction 0.40. The estimated difference for electronic monitoring minus self-report averaged over all visits was -5.0 actuations (95% CI -6.4 to -3.6). The variance components for patient variability was 14.06 and residual variability 50.31, ICC 0.22.

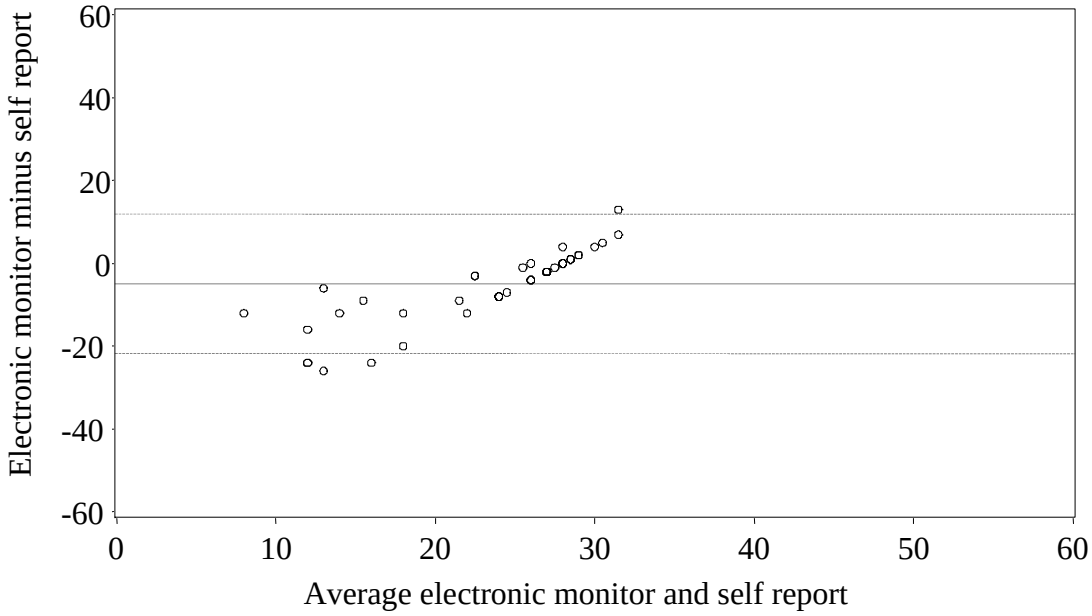
Table 2.3: Self-report and electronic monitoring for the salmeterol separate inhaler

Variable	Visit 2 *	Visit 3 †	Visit 4 ‡	Visit 5 §
Self-reported use of 28 puffs, number of participants (%)	33 (67.4)	30 (60.0)	32 (65.3)	31 (62.0)
Self-report, number of actuations	26.3±3.2	25.9±4.7	25.7±4.2	26.9±3.8
Electronic monitor, number of actuations	21.3±9.9	21.7±10.6	21.8±10.4	19.9±11.5
Electronic monitor minus self-report, number of actuations	-5.0±8.4	-4.2±10.4	-3.9±10.1	-7.0±11.1
Average electronic monitor and self-report, number of actuations	23.8±6.0	23.8±6.4	23.7±6.2	23.4±6.5
Limits of agreement, number of actuations	Plus/minus 16.8	Plus/minus 20.8	Plus/minus 20.2	Plus/minus 22.2

*: N=49; †: N=50; ‡: N=49; §: N=50. Plus/minus values are mean ± SD.

Figure 2.2: Bland Altman plots for the difference between electronic monitor and self report, against the mean of electronic monitor and self report, for the salmeterol inhaler

a) Visit 2

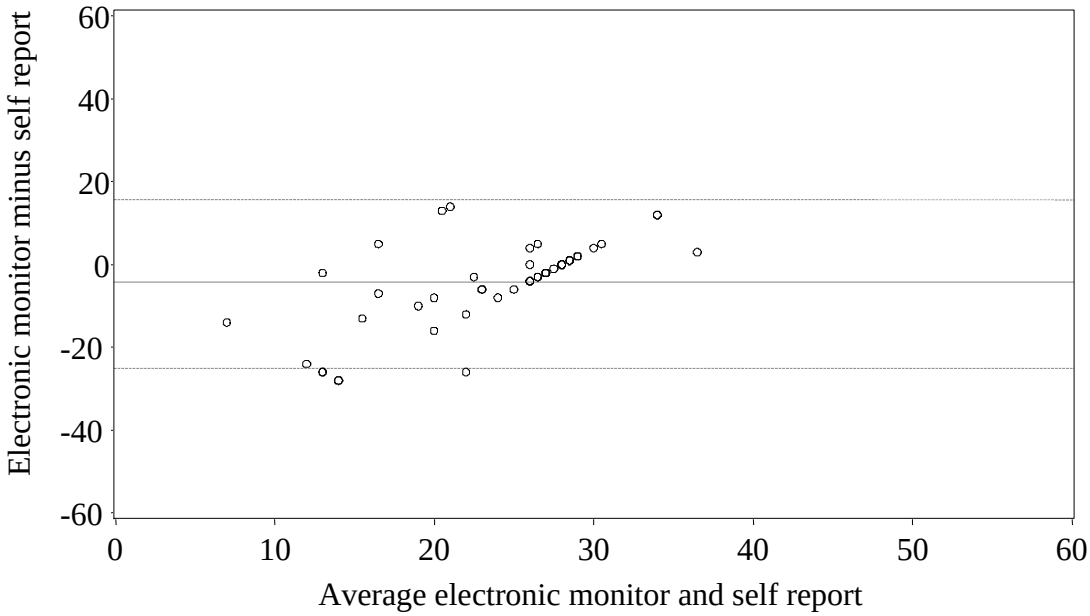


Numbers are actuations

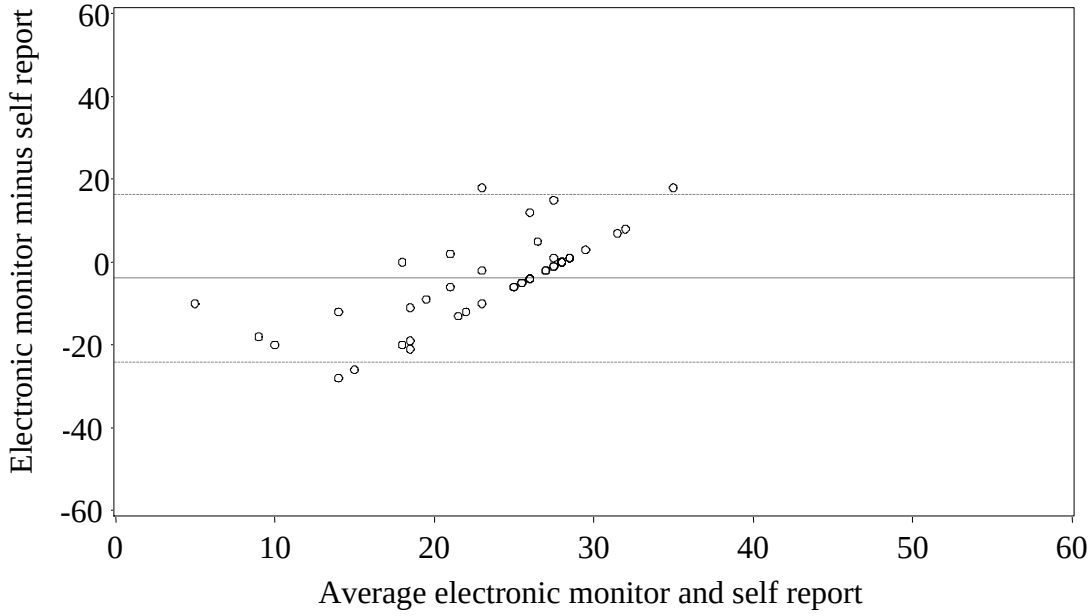
——— : Mean difference between electronic monitor and self-report

— — — : Limits of agreement (plus or minus 2 SD of the mean difference between electronic monitor and self-report)

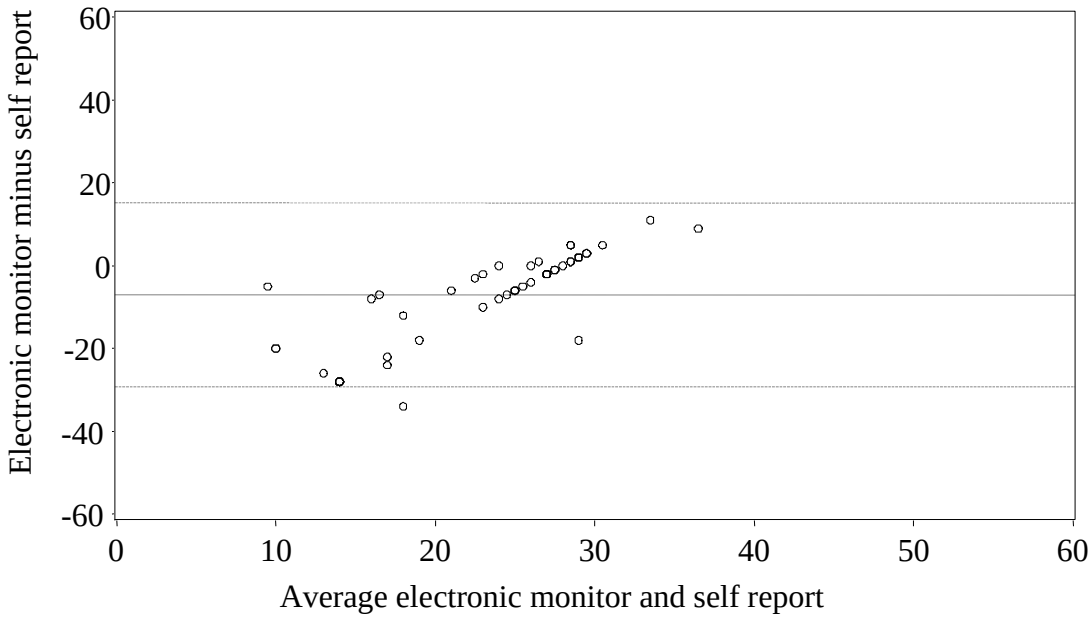
b) Visit 3



c) Visit 4



d) Visit 5


Electronic monitor minus self report
60
40
20
0
-20
-40
-60
0
10
20
30
40
50
60
Average electronic monitor and self report

2.5.3 Fluticasone/salmeterol combination inhaler

Across the four study visits, the mean ± SD of the average of electronic monitoring and self-report was between 24.3 ± 5.7 and 25.0 ± 6.0 actuations (Table 2.4). The mean ± SD of electronic monitoring minus self-report was between -2.2 ± 8.4 and -4.3 ± 9.0 actuations (Table 2.4). Figure 2.3 (a-d) shows Bland-Altman plots for the four study visits. Limits of agreement for electronic monitoring and self-report were wide, ranging between 15.8 and 18.0 actuations. The percentage of participants whose self-reported use was the prescribed 28 puffs was between 63% and 70%. Participants who under-used fluticasone/salmeterol were more likely to over-report actual use, whilst those who over-used were more likely to under-report. The greater the degree of under-use, the greater the magnitude of over-report and the greater the degree of over-use, the greater the magnitude of under-report.

There was no evidence that the difference between electronic monitor and self-report was different at the different visits, p for interaction 0.58. The estimated difference for electronic monitoring minus self-report averaged over all visits was -3.4 actuations (95% CI -4.6 to -2.3). The variance components for patient variability was 11.64 and residual variability 35.20, ICC 0.25.

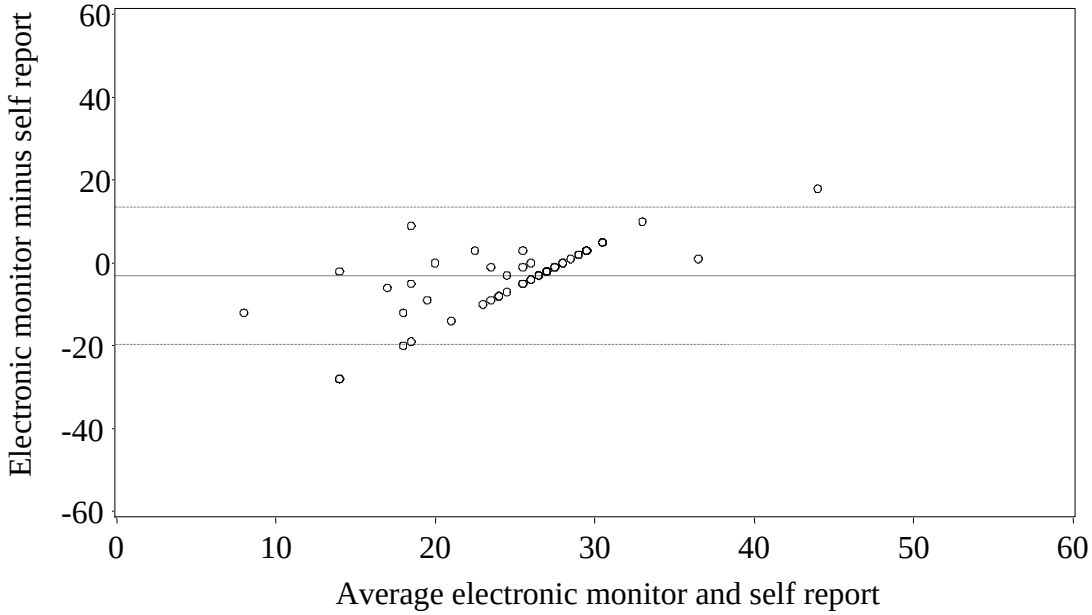
Table 2.4: Self-report and electronic monitoring for the fluticasone/salmeterol combination inhaler

Variable	Visit 2 *	Visit 3 †	Visit 4 ‡	Visit 5 §
Self-reported use of 28 puffs, number of participants (%)	37 (69.8)	34 (66.7)	36 (67.9)	34 (63.0)
Self-report, number of actuations	26.5±4.1	26.5±4.9	26.0±3.6	27.1±4.3
Electronic monitor, number of actuations	23.4±9.5	22.2±9.0	23.8±8.7	23.0±7.6
Electronic monitor minus self-report, number of actuations	-3.1±8.3	-4.3±9.0	-2.2±8.4	-4.1±7.9
Average electronic monitor and self-report, number of actuations	25.0±6.0	24.3±5.7	24.9±5.1	25.0±4.8
Limits of agreement, number of actuations	Plus/minus 16.6	Plus/minus 18.0	Plus/minus 17.4	Plus/minus 15.8

*: N=53; †: N=51; ‡: N=53; §: N=54. Plus/minus values are mean ± SD.

Figure 2.3: Bland Altman plots for the difference between electronic monitor and self report, against the mean of electronic monitor and self report, for the fluticasone/salmeterol combination inhaler

a) Visit 2

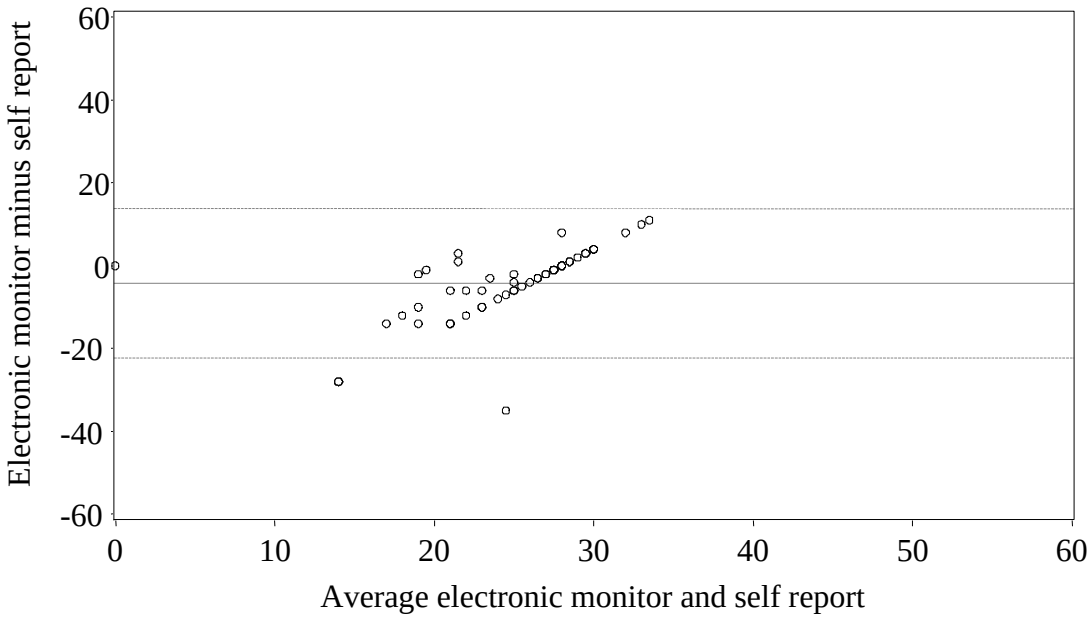


Numbers are actuations

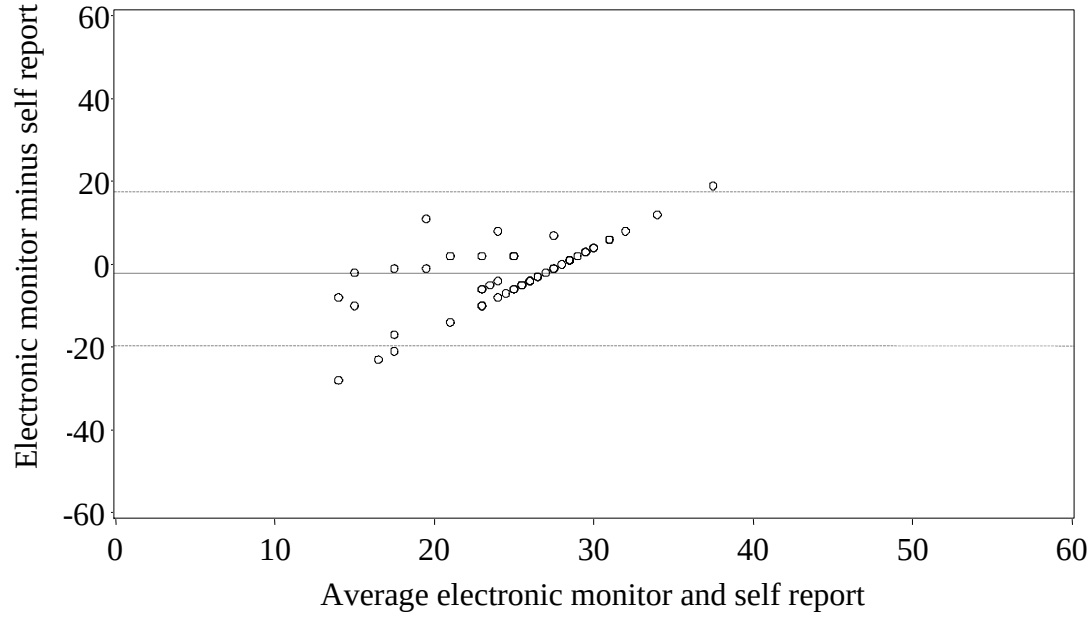
——— : Mean difference between electronic monitor and self-report

— — — : Limits of agreement (plus or minus 2 SD of the mean difference between electronic monitor and self-report)

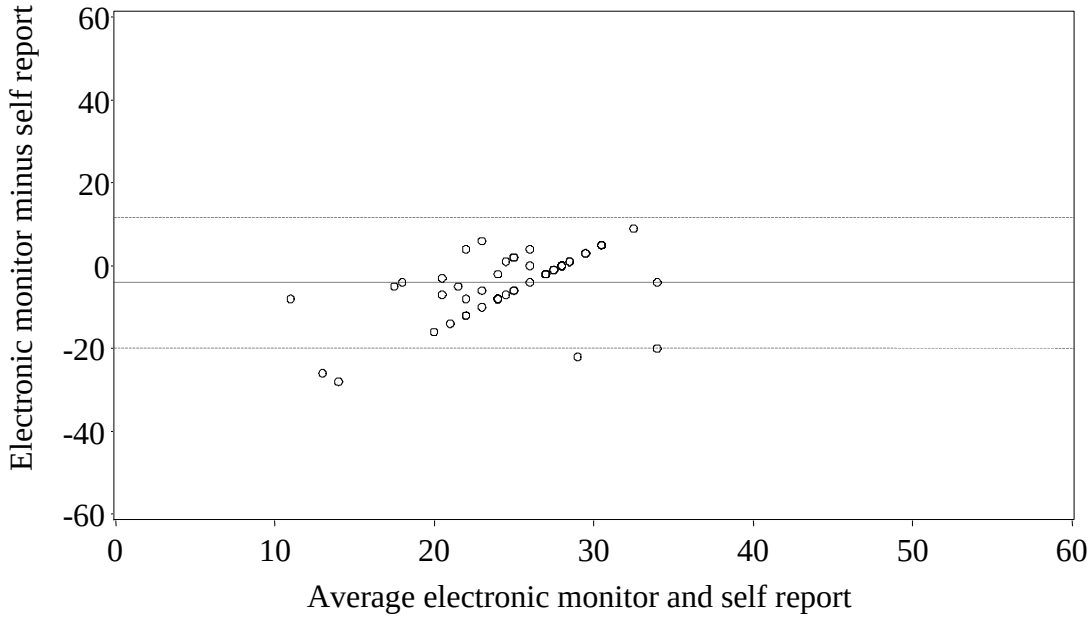
b) Visit 3



c) Visit 4



d) Visit 5


Electronic monitor minus self report
60
40
20
0
-20
-40
-60
0
10
20
30
40
50
60
Average electronic monitor and self report

2.6 Discussion

This study demonstrates that self-report of single and combination ICS and LABA inhaler use was inaccurate in adult asthma patients with relatively high levels of adherence in the setting of an RCT. Participants who under-used their inhaler therapy were more likely to over-report actual use, whereas those who over-used their inhaler therapy were more likely to under-report actual use. Furthermore, the greater the degree of under-use, the greater the magnitude of over-report and likewise, the greater the degree of over-use, the greater the magnitude of under-report. These findings illustrate the limitations of self-reported inhaler use and justify the use of electronic monitoring as the preferred option to measure patterns of inhaled asthma medication use in a clinical trial.

Several conclusions can be drawn from these results. The limits of agreement were wide, ranging from plus or minus 15.8 to 25.6 inhalations, illustrating the inaccuracy of self-report when compared to actual use as measured by electronic monitoring. In addition, self-report consistently over-estimated actual inhaler use by a mean of 2.2 to 8.4 inhalations over a one-week period, with the difference between self-report and electronic monitoring similar with the different medications. These finding are consistent with studies correlating electronic data with self-report of medication use (Foster et al., 2012a; Burgess et al., 2008) and demonstrate the superiority of electronic monitoring compared to self-report.

Patients who under-used their maintenance treatments tended to over-report their use. This may be particularly relevant when using self-report to assess medication use in patients with poor asthma control, when knowledge of adherence to current treatment is important prior to modifying a management regimen. Conversely, participants who over-used their treatment tended to under-report their medication use. Although not assessed in this study, over-use of inhaled asthma medication is most likely to occur with bronchodilator medications which are prescribed to be taken as-required for relief of symptoms (Patel, Perrin and Beasley, 2011; Beasley et al., 2009b; Diette et al., 1999; Windom et al., 1990a). Thus, the use of self-report to assess 'reliever' medication use in patients who over-use their medications is likely to underestimate actual use in this setting.

The greater the degree of under-use of treatment by patients, the greater the magnitude of over-reporting of their use. Similarly, the greater the degree of over-use of treatment, the greater the magnitude of under-reporting of their use. These findings have implications for trials investigating patterns of use of inhaled therapy, as self-report may be particularly unreliable in identifying those patients who either markedly under- or over-use their treatments.

The self-report questionnaire used in this study prompted the participants with the number of inhalations that were prescribed i.e. 28 inhalations during the seven day period. Approximately two-thirds of patients entered this value in the self-report questionnaire, indicating full adherence to prescribed treatment. This may have relevance to the phrasing of self-report questionnaires in a clinical setting, whereby a prompt of the correct answer might affect the response from the patient. The

importance of the approach used during questioning when discussing medication adherence with patients has recently been highlighted in another study (Foster et al., 2012a). Alternatively, electronic monitoring may be used in place of self-report questionnaire in the clinical trial setting.

Though study participants were not explicitly informed about the capabilities of the electronic monitors used in the trial, there is a possibility that some patients became aware that their medication use was being monitored, which may have affected their behaviour. One consequence of this may have been the occurrence of dose dumping, whereby patients actuated their inhaler numerous times within a short period of time in order to simulate adherence to medication use. This is a recognised limitation of electronic monitoring in general (Simmons et al., 2000). This pattern of medication use was identified and removed prior to analysis, in order to minimise that possibility of erroneous data being included in the analysis. The definition of dose dumping (six or more actuations within a five minute period) was more stringent than that used previously (Rand et al., 1992), as this current analysis involved monitoring of fixed-dose maintenance therapy rather than as-required short-acting bronchodilator therapy. However, the identification of dose dumping is limited by the lack of a consensus definition. For patients in whom reliever medication is electronically monitored, this approach may lead to data from actual 'high use' of medication being erroneously removed from the analyses. An alternative approach may be to remove data on the day of study visits prior to performing the analyses, as dose dumping may occur on the day of the study visit (Rand et al., 1992).

2.7 Conclusions

Electronic monitoring is more accurate than self-report in measuring inhaled asthma medication use. Self-report represents the standard method used in clinical practice to assess medication adherence. Knowledge of its limitations will enable clinicians to better understand information provided by this measure of medication use, especially when used to make treatment decisions. In clinical trials where patterns of use of medication are being investigated, the use of electronic monitoring is the preferred option to collect data on actual use of treatment (Foster et al., 2012a; Rand et al., 2012).

2.8 Contributors

The concept, design, data extraction, analysis and interpretation of this study were led by Mitesh Patel with support from Kyle Perrin, Alison Pritchard, Mark Weatherall and Richard Beasley. The current study was supported by a grant from the Health Research Council of New Zealand. Data collection for the original RCT (Perrin et al., 2010) was performed by Kyle Perrin, Alison Pritchard, Mathew Williams, Meme Wijesinghe, Kate James and Richard Beasley. The original RCT (Perrin et al., 2010) was supported by a research grant from GlaxoSmithKline (GSK study no. SAM106689).

This study has been published: Patel, M., Perrin, K., Pritchard, A., Williams, M., Wijesinghe, M., Weatherall, M., & Beasley, R. 2013. Accuracy of patient self report as a measure of inhaled asthma medication use. *Respirology*, 18, 546-552 [with permission to use from the publisher John Wiley & Sons Ltd].

Chapter Three: Smartinhaler Tracker electronic monitor six-month validation study

3.1 Introduction

The Smartinhaler Tracker ('Tracker') is an electronic monitor for use with MDIs which records the date and time (to the nearest second) of MDI actuations. This data are stored on the monitor and can then be uploaded, via the internet, to a website-based database via a USB computer connection and dedicated computer software (Connection Centre, Nexus6 Limited, Auckland, New Zealand).

During the data upload process, a backup copy of the data on the monitor (in Microsoft Excel format) is automatically copied to the computer hard-drive. Therefore, the three elements of the monitoring system are the monitor itself, the database of medication usage retrieved from the monitor and the interface between the two. Satisfactory functioning of all three elements is required for data accuracy. The Tracker has previously been validated for use in short-term bench studies (Chan et al., 2009; Burgess et al., 2006) but no data exist on the accuracy of the monitors over prolonged periods or the reliability of all three elements of the monitoring system, when tested under laboratory conditions.

3.2 Hypothesis

The hypothesis was that provided pre-use checks of monitor function were performed, the Tracker monitors would be highly reliable in recording the number, date and time of MDI actuations when tested over a six-month period under standardised laboratory conditions.

3.3 Aims

The aims of this validation study were:

1. To perform pre-use checks to identify faulty monitors prior to commencing six-month testing.
2. To determine the accuracy of the Tracker monitors in recording the number of MDI actuations over 24-weeks of use, with both ‘high’ and ‘low’ use actuations.
3. To determine the accuracy of the monitor clock.
4. To determine the accuracy of the monitor in recording time and date logs.
5. To determine monitor accuracy in retaining medication usage data over an eight-week period.
6. To assess functioning of the monitor after an eight-week period without use.

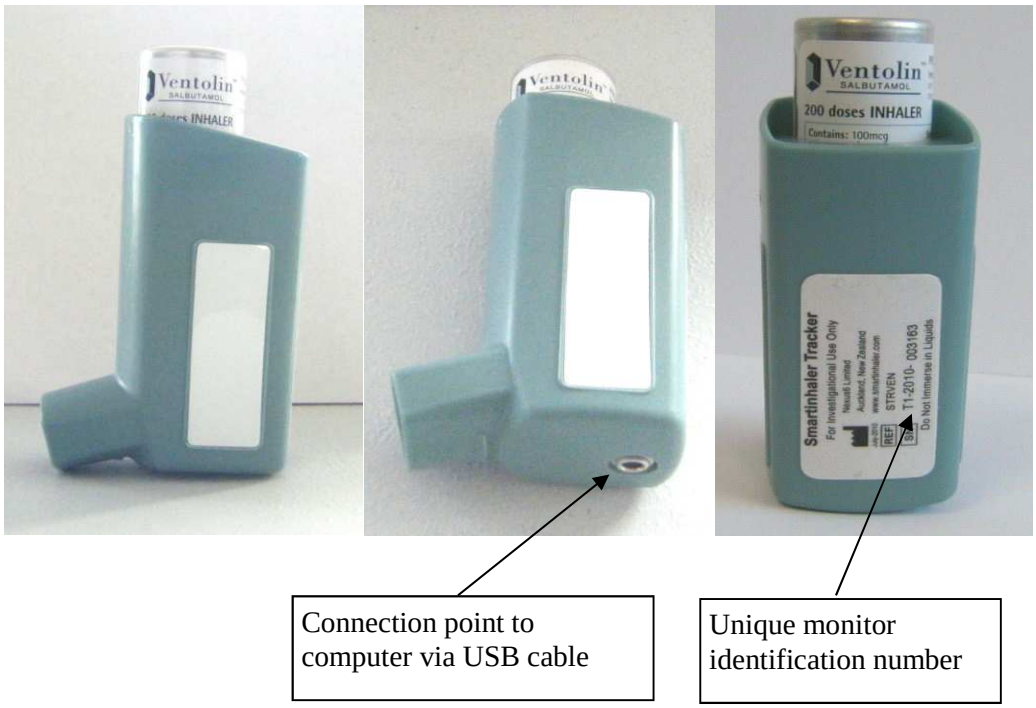
7. To assess the reliability of monitors to not record spurious actuations during an eight-week period without use.
8. To determine the battery life of the monitors over the testing period.
9. To assess the performance of the software used to upload data from the monitors and the accuracy of the website database.
10. To relate these validation study findings to the use of the monitors in the SMART study clinical trial, in order to provide guidance for the trial protocols to maximise data integrity.

3.4 Methods

A total of 22 Tracker monitors were included in this 24-week validation study. Half were loaded with Vannair (budesonide/formoterol 200/6µg per actuation, AstraZeneca Limited, Auckland, New Zealand) medication canisters (Figure 3.1) and half with Ventolin (salbutamol 100µg per actuation, GlaxoSmithKline Limited, Auckland, New Zealand) medication canisters (Figure 3.2). Testing was undertaken at 0, 8, 16 and 24 weeks, to replicate study windows in a 24-week clinical trial. MDI testing was undertaken in a dedicated office area and under standardised conditions each time by two persons together (Mitesh Patel and Richard Beasley).

Figure 3.1: Smartinhaler Tracker for budesonide/formoterol (Vannair MDI)

Figure 3.2: Smartinhaler Tracker for salbutamol (Ventolin MDI)



One investigator was responsible for inhaler actuation whilst the other investigator maintained a paper diary of the number, date and time of actual actuations performed. This method was utilised to minimise the chance of investigator error affecting the interpretation of electronic actuation data.

The key elements of monitor function that were tested are summarised in Table 3.1.

3.4.1 Pre-use checks (Week 0)

22 monitors (11 Vannair and 11 Ventolin) were reset, loaded with a medication canister and then reset again. The reset function was performed by connecting the monitor to the computer via a USB connection and utilising the Connection Centre software; this cleared data from the memory of the monitors and updated the monitor clock. At every canister re-load during the testing process, the monitor was actuated simultaneously in order to ensure correct canister insertion. Monitors were then actuated as follows: two actuations separated by 10 to 20 seconds, repeated once at least two hours later, for two days (total eight actuations). This pattern was chosen to act as an initial screen to identify malfunctioning devices early in the testing process. The monitors were uploaded and the number of actuations together with the date and time of recordings analysed. Functioning monitors went on to complete the remaining testing process.

Table 3.1: Monitor functions tested over the 24-week period

Monitor function tested	Week 0	Week 8	Week 16	Week 24
Reset *	X	X		
Loading with medication canister †	X		X	
Initial screen of monitor ‡	X			
Low use actuations §	X	X		X
High use actuations ‖	X	X		X
Actuation time and date	X	X		X
Upload of data to website	X		X	X
Preview of data ¶		X	X	
Erroneous actuation check during 8-week period without use		X		
Storage of electronic data for an 8-week period			X	
Accuracy of monitors in recording actuations after 8 weeks of no use				X
Comparison of uploaded website data to diary data			X	X
Comparison of computer backup data to diary data			X	X
Monitor clock accuracy over 8 weeks				X
Monitor battery charge				X

*: Data cleared from monitor memory and clock synchronised with computer; †: the monitor was actuated during every canister reload to ensure correct insertion; ‡: initial screen comprised of 2 actuations performed twice per day for 2 days (n=176 actuations); §: low use actuations comprised of 2 actuations performed twice per day on a total of 7 days over the 24-week period (n=560 actuations); ‖: high use actuations comprised of 8 actuations performed three times per day on a total of 3 days over the 24-week period (n=1440 actuations); ¶: visual inspection of data on monitor without uploading of data to website.

3.4.2 High use (Week 0)

Eight actuations were performed, repeated on two other occasions on the same day, with each actuation separated by 10 to 20 seconds (total 24 actuations). This pattern was chosen to reflect 'high' reliever medication usage, for instance, around the time of worsening asthma control.

3.4.3 Low use (Week 0)

Two actuations separated by 10 to 20 seconds, repeated once at least two hours later on the same day (total four actuations). This pattern was chosen to reflect maintenance or 'low' reliever medication use. Monitors were uploaded and canisters removed and re-inserted to simulate canister change. A reset was performed and checked to ensure no actuations were recorded and the monitors were then stored in a locked cabinet without use for eight weeks.

3.4.4 Week 8

The stored monitors were 'previewed' to identify any extra doses that may have been erroneously recorded whilst the monitors were not in use. The preview function allows data on the monitors to be viewed on a computer, without uploading to the central database. The monitors were then reset and previewed to ensure that reset had occurred correctly. Testing for four consecutive days occurred as follows. Days 1 and 2: two actuations separated by 10 to 20 seconds, repeated once at least two hours later on the same day ('low use'). Day 3: eight actuations were performed, repeated on two other occasions on the same day, with each actuation separated by

10 to 20 seconds ('high use'). Day 4: two actuations separated by 10 to 20 seconds, repeated once at least two hours later on the same day ('low use'). Monitors were previewed for data accuracy and then stored for eight weeks with the data stored on the monitor.

3.4.5 Week 16

All data from the monitors was uploaded to the website, thereby checking the accuracy of data retention on the monitors from the previous eight-week period. This also tested the process of data backup to the computer hard drive, the performance of the Connection Centre software and transfer to the website database. The medication canisters were removed and re-inserted. The monitors were previewed and any recorded actuations noted. The monitors were then stored for eight weeks in a locked cabinet without use.

3.4.6 Week 24

Monitors were tested for four consecutive days as per the process in Week 8. This tested the accuracy of monitor function after an eight-week period without use and after a canister change. Data was then uploaded to the website and analysed for accuracy. A measurement of clock discrepancy between the time recorded by the Tracker and an external 'real-time' clock was made. Battery charge was recorded.

3.5 Results

The results of the 24-week testing for all 22 monitors are summarised in Table 3.2.

3.5.1 Pre-use checks

Two of 22 Smartinhalers (9%) failed during the initial screen (one each of budesonide/formoterol and salbutamol) and were subsequently removed from further testing. One of these monitors (loaded with budesonide/formoterol) recorded a correct number of actuations but all date/time logs were incorrect. The first two actuations were recorded at the correct date but a time that was incorrect by four hours in the future. The next two actuations, which were performed two hours later, were recorded as having occurred over 12 hours after the actual time. The other monitor (loaded with salbutamol) recorded the correct number and time of doses, but with an incorrect date for all actuations. The date was incorrect by 10 years in the past.

3.5.2 Accuracy of recording the number of MDI actuations

Overall accuracy in recording the number of actuations performed throughout the entire testing period was 99.7% (2170 of 2176 doses correctly recorded). During simulated maintenance or low reliever use, accuracy of recorded actuations was 98.9% (554 of 560 doses correctly recorded (i.e. six low use doses not recorded). During simulated high use, all actuations were correctly recorded (all 1440 doses recorded).

Table 3.2: Results of the testing process

Monitor function tested	Accuracy
Number of monitors completing full testing period (%)	20 (91%) *
Overall accuracy in recording number of actuations over 24 weeks (%)	2170 recorded of 2176 actuations performed (99.7%)
Accuracy during low use † (%)	554 recorded of 560 actuations performed (98.9%)
Accuracy during high use † (%)	1440 recorded of 1440 actuations performed (100%)
Accuracy at Week 24 (%) *versus* Accuracy at Weeks 0 to 16 † (%)	Week 24: 716 recorded of 720 actuations performed (99.4%) Weeks 0 to 16: 1278 recorded of 1280 actuations performed (99.8%)
Accuracy in recording actuation time & date ‡ (%)	2160 actuations accurate of 2176 performed (99.3%)
Number of extra actuations recorded (% of total)	8 extra actuations § (0.37%)
Number of monitors in which extra or missed actuations occurred during testing	2 Ventolin Trackers
Number of erroneous actuations during 8 weeks without use	0
Data retention for 8 weeks (%)	100%
Accuracy after 8 weeks of no use (%)	716 recorded of 720 actuations performed (99.4%)
Accuracy of website data (%)	100%
Accuracy of computer backup of data (%)	100%
Mean ± SD monitor clock accuracy (mm:ss) ‖	05:10 ± 00:52
Battery charge at Week 24	Full charge for all monitors

*: 1 Vannair and 1 Ventolin monitor failed during Week 0 Initial Screen
†: Accuracy in recording the number of actuations performed
‡: Accommodating clock drift
§: 4 during testing period and 4 outside of testing period (at the time of computer connection)
‖**:** Estimate of discrepancy between monitor clock and actual time occurring over 8 weeks
m: minutes; s: seconds

The total number of extra actuations erroneously recorded was eight (0.37% of total number of actuations performed). Of these eight extra actuations, four (50%) were recorded at the time of computer connection (e.g. preview or upload) and outside of the testing period. A further three occurred during low use actuation and one during high use actuation. The extra or missed actuations that occurred during testing were in the same two salbutamol Trackers.

Monitor accuracy at Week 24 (716 recorded of 720 actuations performed) was comparable to that during the first 16 weeks of use (1278 recorded of 1280 actuations performed).

3.5.3 Accuracy of the monitor clocks

An estimate of mean ± SD time drift between the actual time and the Tracker clock times was 5 min 10 seconds ± 52 seconds over an eight-week period.

3.5.4 Accuracy in recording date and time of actuations

Accommodating the drift in monitor clocks over time, overall accuracy in the 22 monitors in recording date and time was 99.3% (2160 actuations correct of 2176 performed). With identification and removal of the two faulty monitors during the pre-use checks, all the 20 monitors completing the full 24-week testing period were 100% accurate in recording date and time.

3.5.5 Accuracy in retaining data over an eight-week period

Monitors were 100% accurate in retaining stored electronic logs for an 8-week period, with no additional logs recorded during this period.

3.5.6 Function after an eight-week period without use

716 of 720 actuations (99.4%) were recorded correctly after an eight-week period without use.

3.5.7 Reliability in not recording spurious actuations during an eight-week period without use

None of the monitors recorded spurious logs during an eight-week period without use.

3.5.8 Battery life during the testing period

Battery charge was at full capacity (4 bars out of 4) in all monitors over the 24-week period.

3.5.9 Performance of the computer software and website database

Data accuracy on the backup Excel files saved onto the hard drive of the computer and on the website database was compared with the written diary; transfer and storage of data was 100% accurate. The Connection Centre software performed reliably to preview, upload and reset the monitors.

3.6 Discussion

This study has demonstrated that the Smartinhaler Tracker electronic monitors are accurate devices for measuring inhaled asthma medication use over a 24-week period, in a strictly controlled laboratory setting, providing initial pre-use checks are performed. The study has provided information on the monitors' reliability and accuracy in a variety of domains and builds on prior knowledge gained from electronic monitoring use (Spector et al., 1986). Additionally, the validation process tested three key elements of data acquisition: monitor accuracy, integrity of the stored database of information retrieved from the electronic monitor and the software interface between the monitor and the database. The information gained from this validation process has helped to guide the clinical trial protocols to identify malfunctioning devices, both before and during patient use, in the primary RCT.

The Smartinhaler Trackers proved to be highly accurate in recording MDI actuations and their time and date, in keeping with prior short term validation studies (Chan et al., 2009; Burgess et al., 2006). This monitoring system therefore allows for accurate monitoring of MDI actuation in the context of a clinical trial and allows data on medication usage to be collected in both maintenance/low use and high use settings. These results allow confident interpretations to be made from recorded data, especially in situations where there is particularly low use (e.g. non-adherence) or high use (e.g. over-use) of medication.

In addition, the monitors were highly reliable in retaining stored data for an 8-week period and in functioning accurately after 24 weeks of testing. This simulates their use in a clinical trial setting, whereby they would be required to retain stored data in between study visits and may be used over a prolonged period. Using the validation process described above, the monitors did not record spurious logs during periods without use. This reflects the trial setting whereby patients may use their inhalers intermittently, particularly if given access to more than one inhaler to use simultaneously. Storage of monitors without use might also occur prior to trial dispensing or in the case of emergency 'backup' inhalers given to trial participants which remain unused for a period of time. In both of these instances, the validation process has demonstrated that spurious logs are unlikely to occur.

Monitors were also reliable in functioning accurately after an eight-week period of storage. In the trial setting, emergency or spare MDIs may be stored for a period of time and then used or dispensed without any further checks of function. Battery charge was normal for all monitors. In the trial setting, the number of actuations recorded per monitor is likely to be greater than the number per monitor recorded in this laboratory study (108 actuations); hence, this may impact on battery life and within-trial checks of battery function may be considered.

An important part of this validation process was to also test the integrity of the software used to upload the data from the monitors as well as the database of information created from monitor uploads. This is of particular relevance for multicentre trials, where multiple computers in different locations may be used to upload information. It was noted that the four extra recorded actuations that

occurred outside of the testing period happened around the time of connection of the monitor to the computer for upload or preview, suggesting that either a software issue or unintentional actuation by the investigator was responsible. On further discussion with the monitor manufacturer, it was suggested that a cable error in the connection from the monitor to the computer might also be a factor leading to spurious extra actuations. This information may have implications for the data analysis process. Data recorded on the day of the study visit could be removed from the final database, in order to reduce the chance of erroneous actuations being included in the analysis. This may also have the effect of removing dose-dumping data from the analysis (Rand et al., 1992). Apart from this issue, the software interface and data storage spreadsheets were found to be robust and accurate.

The occurrence of extra (or duplicate) actuations occurring during testing was extremely low (4/2176 actuations). Three of these four logs were during low use testing and one was during high use testing. In the RCT setting, the occurrence of these duplicate actuations may occur equally in both groups due to the process of random allocation. Considered together, this further supports the view that data recorded by these monitors reflects actual use of medication and that the occurrence of duplicate actuation logs is unlikely to affect interpretation of study results.

The results of the testing process described above can have significant implications for clinical trial conduct utilising these monitors. On initial screening, it was identified that one salbutamol and one budesonide/formoterol MDI incorrectly recorded the time or date of actuations, even though the number of actuations performed was recorded correctly. An initial abbreviated Quality Control protocol

may be incorporated into the trial process, in which all monitors are tested for accuracy in recording the number of actuations and date/time prior to use by participants. This would allow faulty monitors to be removed prior to trial use. This study did not assess the 'real-world' use of the monitors. Although accuracy was high in monitors that passed the initial screening, there is a potential for malfunction during real-life use by patients. For example, due to its electronic components, the monitor may be vulnerable to the effects of moisture, which could affect its performance in recording actuations. Additional checks of monitor function by investigators prior to study visits may help to identify monitors damaged during participant use. Updates to the software and connecting cables may be implemented, to reduce the possibility of spurious doses being recorded at the time of computer connection. Data backup processes may be implemented to both safeguard uploaded data and allow malfunctioning monitors to be returned to the manufacturer for data retrieval.

A specific limitation of the Trackers, inherent to most electronic MDI monitors, is that they record inhaler actuation, but not necessarily medication inhalation. Thus, there is the possibility that some patients may actuate the MDI but not necessarily inhale the medication. Prior validation studies have suggested that incorrect loading of the inhaler with a medication canister may be responsible for missed actuations (Chan et al., 2009; Burgess et al., 2006). To address this issue, the MDI was actuated every time a canister insertion was performed, to ensure correct loading of the canister.

3.7 Conclusions

The Tracker electronic monitors are highly accurate in recording MDI actuations in a laboratory setting, providing initial pre-use checks are performed. Validating the function of these electronic monitors has allowed an understanding of their strengths and limitations and has helped to inform the study protocols for their use in the SMART study RCT, in order to safeguard data acquisition and minimise erroneous data collection.

3.8 Key recommendations for the Quality Control protocols for the SMART study RCT

Based on the above validation process, the key points to be considered for inclusion into the protocols for the use of these monitors in the SMART study RCT are as follows:

1. Pre-use checks performed at the coordinating trial site, involving two actuations separated by 10 to 20 seconds, repeated once at least two hours later, are recommended for all MDIs prior to trial use.
2. MDIs passing pre-use checks can be stored and then dispensed to participants at Visit 1 without a requirement for additional checks.
3. Backup emergency MDIs dispensed to participants do not require repeat testing if they remain unused.

4. Spare MDIs provided to sites may be dispensed without a requirement for additional checks.
5. Use of an updated cable to connect monitors to a computer may reduce the occurrence of spurious actuations due to cable errors.
6. Within-trial checks of monitor accuracy (for example, in recording the number/date/time of actuations and battery life) at Visits 2, 3 and 4 may help to identify monitors malfunctioning or damaged after the pre-use checks.
7. Checks of monitor clock accuracy on return of inhalers from participants may identify erroneous data prior to upload to the central database.
8. Creating backup copies of the inhaler use data on the computer hard drive may provide a safety net in case of website malfunction and allow data to be saved in an alternative format (e.g. compact disc).
9. Medication canisters should be inserted firmly into the monitors at every canister reload to ensure correct placement.
10. Removal of data on the day of the study visit could prevent the minority of erroneous actuations occurring during monitor connection to the computer from being included in the analyses.

3.9 Acknowledgements

The concept and design of this validation study were performed primarily by Mitesh Patel and Richard Beasley, with input from Amy Chan. Data collection was

performed by Mitesh Patel and Richard Beasley. Analysis and data interpretation were performed by Mitesh Patel, Janine Pilcher, Amy Chan, Kyle Perrin and Richard Beasley.

This study has been published: Patel, M., Pilcher, J., Chan, A., Perrin, K., Black, P., & Beasley, R. 2012. Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: Implications for asthma clinical trial use. *J Allergy Clin Immunol*, 130, 1420-1422 [with permission to use from the publisher Elsevier].

Chapter Four: Methods for the SMART study randomised controlled trial

4.1 Overview

The study was a 24-week, open-label, parallel-group, multicentre randomised controlled trial of the efficacy and safety of SMART versus Standard therapy in adult asthma patients at risk of severe exacerbations. The study was conducted at four primary healthcare practices and one hospital in New Zealand.

The two treatments were:

1. The 'SMART' group: 200/6µg budesonide/formoterol MDI (Vannair, AstraZeneca NZ Limited, Auckland, New Zealand; this is the MDI formulation of Symbicort Turbohaler), two actuations twice daily as maintenance with one extra actuation as-needed for relief of symptoms.

2. The 'Standard' group: 200/6µg budesonide/formoterol MDI, two actuations twice daily as maintenance with one to two actuations of 100µg salbutamol MDI (Ventolin, GlaxoSmithKline NZ Limited, Auckland, New Zealand) as-needed for relief of symptoms.

The trial was prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12610000515099). The study protocol is included in Appendix A.

4.2 Participants

4.2.1 Inclusion criteria

The inclusion criteria were:

1. Physician's diagnosis of asthma.
2. Age 16 to 65 years.
3. Current prescription for ICS.
4. No change in the ICS dose in the preceding month. The rationale for this inclusion criterion was to allow a period of stability prior to enrolment for patients with a recent change in ICS dose. Patients were eligible one month after the ICS dose change.
5. At least one asthma exacerbation in the preceding year. This was defined as a presentation to a General Practice (GP) or ED resulting in a prescription of oral corticosteroids and/or treatment with spacer-delivered or nebulised bronchodilator, or self-administration of prednisone for asthma for at least three days. The rationale for the use of this definition for an asthma exacerbation was to allow enrolment of patients with prior moderate or severe asthma exacerbations (Reddel et al., 2009).

4.2.2 Exclusion criteria

The exclusion criteria were:

1. Onset of respiratory symptoms after the age of 40 in current or ex-smokers with ≥10 pack-year smoking history. The purpose of this exclusion criterion was to reduce the chance of patients with chronic obstructive pulmonary disease (COPD) being enrolled into the study.
2. Diagnosis of COPD, interstitial lung disease, or bronchiectasis. The purpose of this exclusion criterion was to screen out any patients in whom asthma was not the primary respiratory diagnosis.
3. Diagnosis of congestive heart failure. The rationale for this exclusion criterion was to screen out any patients with left ventricular failure, in whom use of reliever inhaler therapy may have been due to misattributed symptoms from heart failure.
4. Unstable coronary artery disease or unstable angina. The purpose of this exclusion criterion was to screen out patients at high short-term risk of acute ischaemic cardiac events, in whom the risks of beta-agonist therapy may be greater (Au et al., 2000).
5. Atrial fibrillation or other cardiac arrhythmias. The purpose of this exclusion criterion was to screen out patients with diagnosed cardiac arrhythmias, in whom there may be an increased risk of development of pathological tachycardias following high-dose beta-agonist use (Kung, Croley and Phillips, 1987).

6. Use of an at-home nebuliser [unless patients agreed to withhold nebuliser use for the study duration]. The rationale for this exclusion criteria was to reduce the possibility of concurrent nebulised beta-agonist use during study participation, as this may have increased the risk of delay in seeking medical help by patients during worsening asthma (Sears et al., 1986).
7. Treatment with oral prednisone in the previous four weeks. The rationale for this exclusion criterion was to allow a period of stability prior to enrolment, for patients with a recent severe asthma exacerbation. Patients were eligible four weeks from the start of their course of prednisone.
8. Uncontrolled depression or anxiety disorder. This exclusion criterion was included to screen out patients with severe depression or anxiety, who may not have been able to meet the requirements of the study visits and trial protocol due to their illness.
9. Malignancy with life expectancy of less than one year.
10. Unwilling or unable to switch from current asthma treatment regimen or management plan.
11. Inability to understand the study requirements and/or unwillingness to give consent to participate in the study.
12. Any other safety concern at the investigator's discretion.

4.3 Study sites

The trial was conducted at three GP practices [Henderson Medical Centre, Auckland, New Zealand; CentralMed General Practice, Tauranga, New Zealand; Papamoa

Pines Medical Centre, Tauranga, New Zealand], one Māori primary healthcare clinic [Tu Kotahi Māori Asthma Trust, Lower Hutt, New Zealand] and one hospital site [MRINZ, Wellington Regional Hospital, Wellington, New Zealand] (Table 4.1).

4.3.1 Recruitment of participants at the distant sites

Two GP practices [Henderson Medical Centre and CentralMed General Practice] recruited participants from their patient databases and from advertising in the local community. One GP practice [Papamoa Pines Medical Centre] recruited solely from its patient database. The Māori primary healthcare clinic recruited from its patient database.

4.3.2 Recruitment of participants at the MRINZ site

The MRINZ site recruited from ED and hospital attendance databases at two secondary-level hospitals [Wellington Regional Hospital and Hutt Hospital], local GP databases and from community advertising.

Table 4.1: SMART study sites

Site	Site lead investigator	Site investigators
Auckland Henderson Medical Centre	Dr Rodney Marks	Dr Bill Mackey
		Dr Vikky Qi
		Clare McGuinness-Goodwin (practice manager)
		Tyronne Tranquilino (Nurse Manager)
		Dr Dirk Venter
Tauranga CentralMed General Practice	Dr Andrew Corin	Dr Andrew Corin
		Dr Colin Helm
		Dr Chris Tofield
Tauranga Papamoa Pines Medical Centre	Dr Davitt Sheahan	Dr Davitt Sheahan
Lower Hutt Tu Kotahi Māori Asthma Trust	Cheryl Davies	Ann Smith (Specialist Nurse)
		Dr Mitesh Patel
Wellington MRINZ	Dr Mitesh Patel (trial coordinating investigator)	Dr Mitesh Patel
		Dr Janine Pilcher
		Alison Pritchard (I.T. manager)
		Tanya Baker (clinical trials manager)
		Denise Fabian
		Maureen Stretch
		Mathew Williams
		Dr Kyle Perrin
		Dr Justin Travers
		Professor Mark Weatherall (study biostatistician)
		Professor Richard Beasley

Hospital patient database searches were performed for asthma patients attending ED or who were directly admitted to the wards at Wellington Regional Hospital or Hutt Hospital for the preceding year. Patients who were aged 16 to 65 were sent a letter inviting them to contact the MRINZ if they were interested in learning more about study participation. Database searches were repeated every six months from July 2010 to July 2011.

GPs at several Wellington medical centres were contacted and consent was requested to perform database searches for potentially eligible participants. Searches were performed at Onslow Medical Centre, Karori Medical Centre, Ngaio Medical Centre, Brooklyn Central Health Medical Centre and Wadestown Medical Centre. Potentially suitable patients were sent a letter from their GP informing them of the study and were asked to contact the MRINZ via email, freephone telephone number or pre-paid return envelope if they wished to find out more about the study.

Community advertising was undertaken using posters in local libraries and community centres and by using flyers in local GP practices and after-hours medical centres. Information about the study was also available on the MRINZ website.

Patients had the option of attending study visits at the MRINZ offices at Wellington Regional Hospital or Bowen Hospital, at the Respiratory Clinic at Hutt Hospital, or at their home or workplace.

4.4 Study procedures

4.4.1 Initial screen

Potentially eligible patients were provided the participant information sheet (Appendix B). These patients were then asked initial screening questions relating to the inclusion/exclusion criteria and a date/time was arranged for Visit 1. Patients continued to take their regular inhaled therapy prior to all study visits, without being required to withhold their medication prior to spirometry. Patients were asked to bring all their current inhalers with them to their first study visit, in order to replace them with study medication.

4.4.2 Visit 1 (Week 0)

At first study visit, written consent was obtained prior to any study-specific procedures being performed (Appendix B). The participant information sheet was discussed with patients. The patient's demographics and medical and medication history were taken and the patient's eligibility for the trial confirmed according to the inclusion and exclusion criteria. Spirometry (FEV_1 and FVC) was performed according to a standardised protocol. The ACQ-7 (Juniper et al., 1999) and Satisfaction with Asthma Treatment Questionnaire (SATQ) (Campbell, Kiebert and Partridge, 2003) were completed. All pre-study inhalers were collected from patients.

Patients were randomised to SMART or Standard treatment and study inhalers incorporating electronic monitoring were provided according to their study group [see Section 4.6 for details on randomisation]. All participants were given standardised written asthma self-management plans relating to their randomised group [see Section 4.8] and had their inhaler technique checked. Spacers were dispensed to any patients unable to demonstrate adequate MDI inhaler technique after training. Patients who used peak-flow monitoring prior to study entry continued to do so during their study participation. Written advice on the care of the study inhalers was provided (Appendix C). An appointment card identifying the patient as a participant in a clinical trial was provided, onto which any courses of systemic corticosteroids taken for asthma could be recorded (Appendix C). Participants remained under the care of their usual primary care physicians throughout the study. A letter was sent to the patient's GP with details of the study treatment, a copy of the self-management plan and contact details for the study investigator.

4.4.3 Visits 2, 3 and 4 (Weeks 3, 10 and 17)

At Visits 2 to 4, study participants were asked about any asthma exacerbations, ED visits or hospital admissions occurring since the preceding visit. Exacerbation data, dose and duration of corticosteroid therapy for asthma exacerbations and unscheduled consultations for asthma were collected from patient record (using events noted contemporarily on the patient's study appointment card), spontaneous report and answers to standardised questions at study visits:

‘Since the last study visit, have you taken a course of systemic steroids for your asthma?’

‘Since the last study visit, has troublesome asthma led you to seek unplanned/urgent help for your asthma?’

‘Have you needed to attend ED for your asthma?’

Cross-checks with primary care GP databases and hospital records were performed if there was uncertainty about dates and/or doses. A conversion factor of 100mg intravenous (IV) hydrocortisone to 25mg oral prednisone was used for IV corticosteroid doses.

The ACQ-7 was completed and spirometry was performed. The inhalers previously dispensed were collected from the participants and replacement inhalers issued [see Chapter 5 for full details].

In addition, at Visit 3, asthma self-management plans were reviewed with the patient and inhaler technique was re-checked.

4.4.4 Visit 5 (Week 24)

At Visit 5, study participants were asked about asthma exacerbations as above. ACQ-7, SATQ and spirometry were completed. All previously dispensed inhalers were collected from participants. Participants who wished to continue on their study asthma medication were advised to attend their GP for review. In order to prevent deterioration in their asthma control in the intervening time, participants had the

option of being provided with a budesonide/formoterol and salbutamol inhaler to use whilst awaiting this appointment. A letter was sent to the patient's GP informing them of the patient's study completion.

A summary of the clinic visits and schedule of assessments is shown in Table 4.2.

4.5 Electronic monitoring of MDI use

Smartinhaler Tracker electronic monitors (Nexus6 Limited, Auckland, New Zealand) were incorporated in all Vannair and Ventolin MDIs dispensed in the study. These validated monitors measure the number, date and time of MDI actuations (Patel et al., 2012; Burgess et al., 2006). Participants were told that the total number of actuations from their inhalers was measured, but not of these additional recording capabilities. The rationale for this was to minimise the influence that monitoring adherence may have had on participant behaviour. Covert monitoring was considered ethically acceptable as the risks to participants were minimal and this approach allowed the collection of information in a non-biased form (Rand and Sevick, 2000).

A comprehensive trial quality control programme was implemented in which all monitors were tested for accuracy prior to dispensing and during the full study period [see Chapter 5].

Table 4.2: Schedule of clinic visits and assessments

Visit Number	**1**	**2**	**3**	**4**	**5**
Week	**0**	**3**	**10**	**17**	**24**
Informed consent	X				
Demographics and medical history	X				
Medication history	X				
Eligibility criteria assessment	X				
ACQ-7	X	X	X	X	X
SATQ	X				X
Spirometry (FEV_1 & FVC)	X	X	X	X	X
Randomisation	X				
Self-management plan provided	X				
Inhaler technique checked	X		X		
GP informed of study participation	X				
Appointment card provided with integrated section to record steroid use	X	X	X	X	
Text/telephone reminder of study visit	X	X	X	X	X
Adverse events and concomitant medications review		X	X	X	X
Asthma exacerbations review		X	X	X	X
Dispense study treatment	X	X	X	X	
Inhaler download		X	X	X	X
Validation of electronic monitor		X	X	X	X
Trial completion					X
Patient provided treatment to use whist awaiting GP appointment					X
GP informed of completion of study					X

Each actuation log was stored on the monitor and data was uploaded via a USB computer connection and dedicated software after study clinic visits, to a website-based database via the internet.

All MDIs were actuated during the pre-study testing process. Participants were advised not to perform 'test' actuations, share inhalers, or use non-study inhalers. Participants were also advised not to self-administer multiple MDI actuations as a single high dose via spacer, as a substitute for nebulised therapy.

Participants were able to use their study MDIs concurrently during the study window if they wished. All participants were asked to keep their MDIs free from moisture during trial participation and were reminded not to discard used or empty inhalers. Investigators asked participants about their use of non-study inhalers and sharing of study inhalers at Visits 2 to 5 using the following questions:

> 'Have there been any changes in your asthma medication use since the last visit?'
>
> 'Have you used any non-study asthma medication in the prior 7 weeks?'
>
> 'Has anyone else used your study inhaler apart from you?'
>
> 'Have you had any problems with the inhaler device?'

4.6 Randomisation, allocation concealment and masking

Randomisation was one-to-one, using a computer generated sequence, with fixed-size balanced blocks of eight per site. The randomisation schedule was prepared by the study statistician, who was independent of the investigators undertaking study visits. The schedule was provided to persons independent of the investigators undertaking study visits, who prepared the randomisation envelopes. Opaque, sealed, numbered envelopes were provided to study sites and were opened by investigators undertaking study visits in sequence, once informed consent had been obtained, eligibility had been confirmed and baseline clinic measurements had been recorded.

An open-label trial design was required to be able to reflect real-world clinical practice. All participants, investigators and the statistician were not masked to group assignment.

4.7 Dose determination

Maintenance treatment was with budesonide/formoterol 200/6µg two actuations twice a day for all participants.

4.7.1 Rationale

As patients at risk of severe asthma exacerbations and poor asthma control were the target patient group for this study, GINA Step 4/BTS Step 3 (SIGN/BTS, 2012; GINA, 2011) therapy (medium dose ICS with LABA) was used as the appropriate maintenance treatment for the anticipated baseline level of asthma control.

4.8 Asthma self-management plans

The SMART plan was based on the National Asthma Council Australia 'My Symbicort SMART Asthma Action Plan' (National Asthma Council Australia, 2013). Two versions of this plan, symptom-based or peak-flow based, were used (Figure 4.1 and Figure 4.2 respectively).

The Standard plan was based on the Asthma and Respiratory Foundation of New Zealand 2004 plan (Holt et al., 2004). Two versions of this plan, symptom-based or peak-flow based, were used (Figures 4.3 to 4.6).

As per their self-management plans, participants were advised to seek review from their GP, after-hours clinic or ED in the setting of worsening asthma and every time systemic corticosteroids were commenced. Self-management plans suggested a dose of 40mg of prednisone for five days for an asthma exacerbation, but the final decision was as per the treating physician.

Figure 4.1: SMART symptoms plan

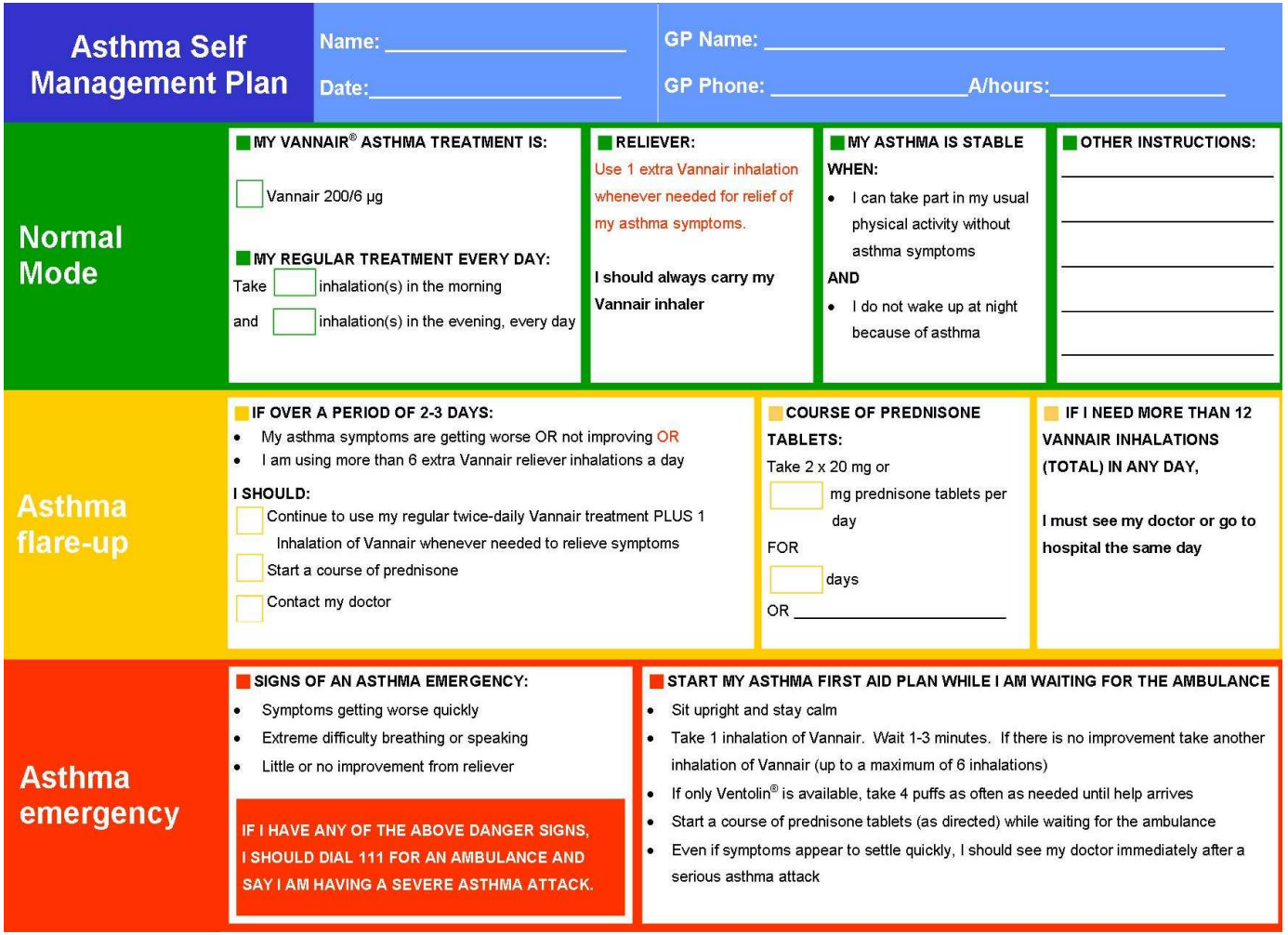


Figure 4.2: SMART peak flow plan

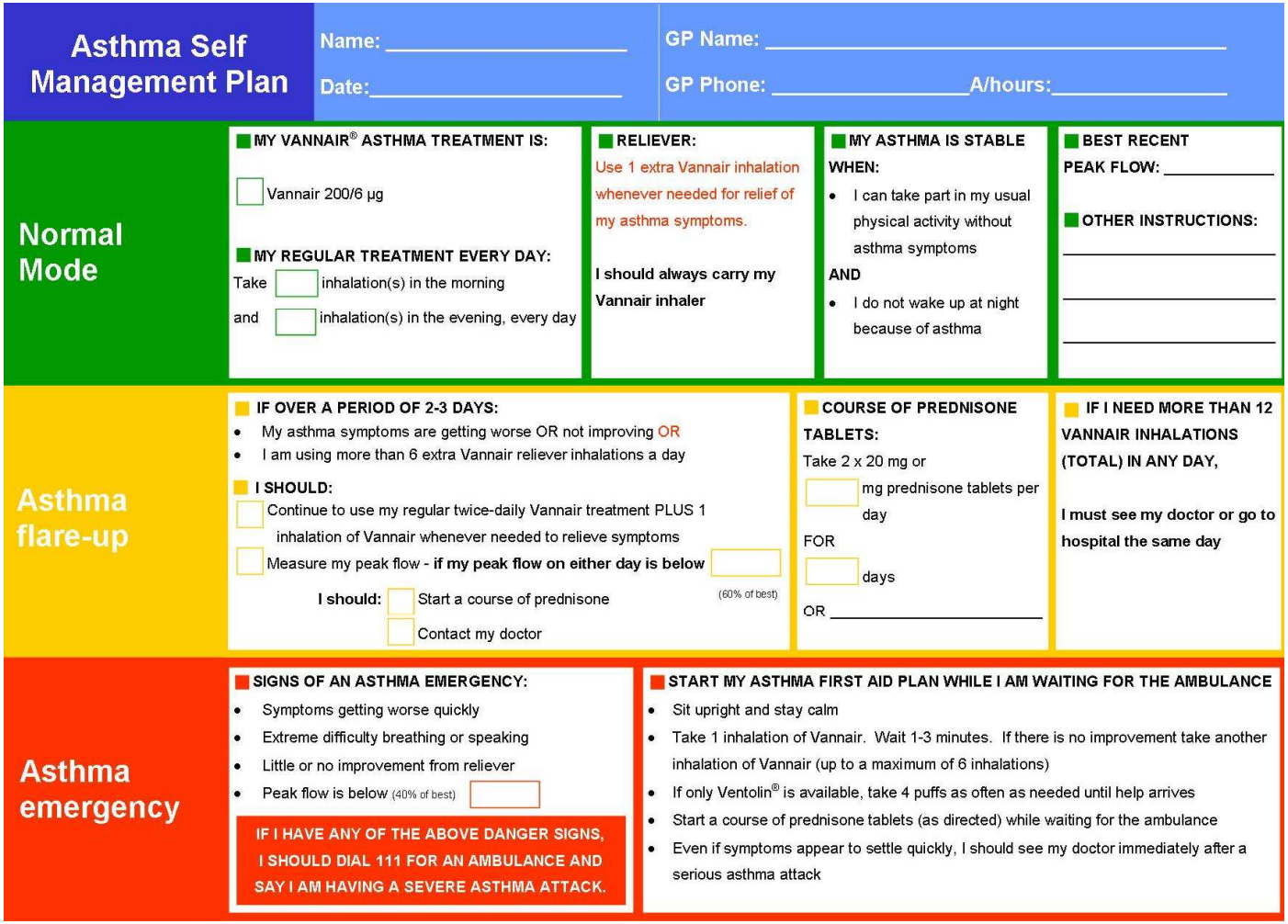


Figure 4.3: Standard Symptoms plan - front

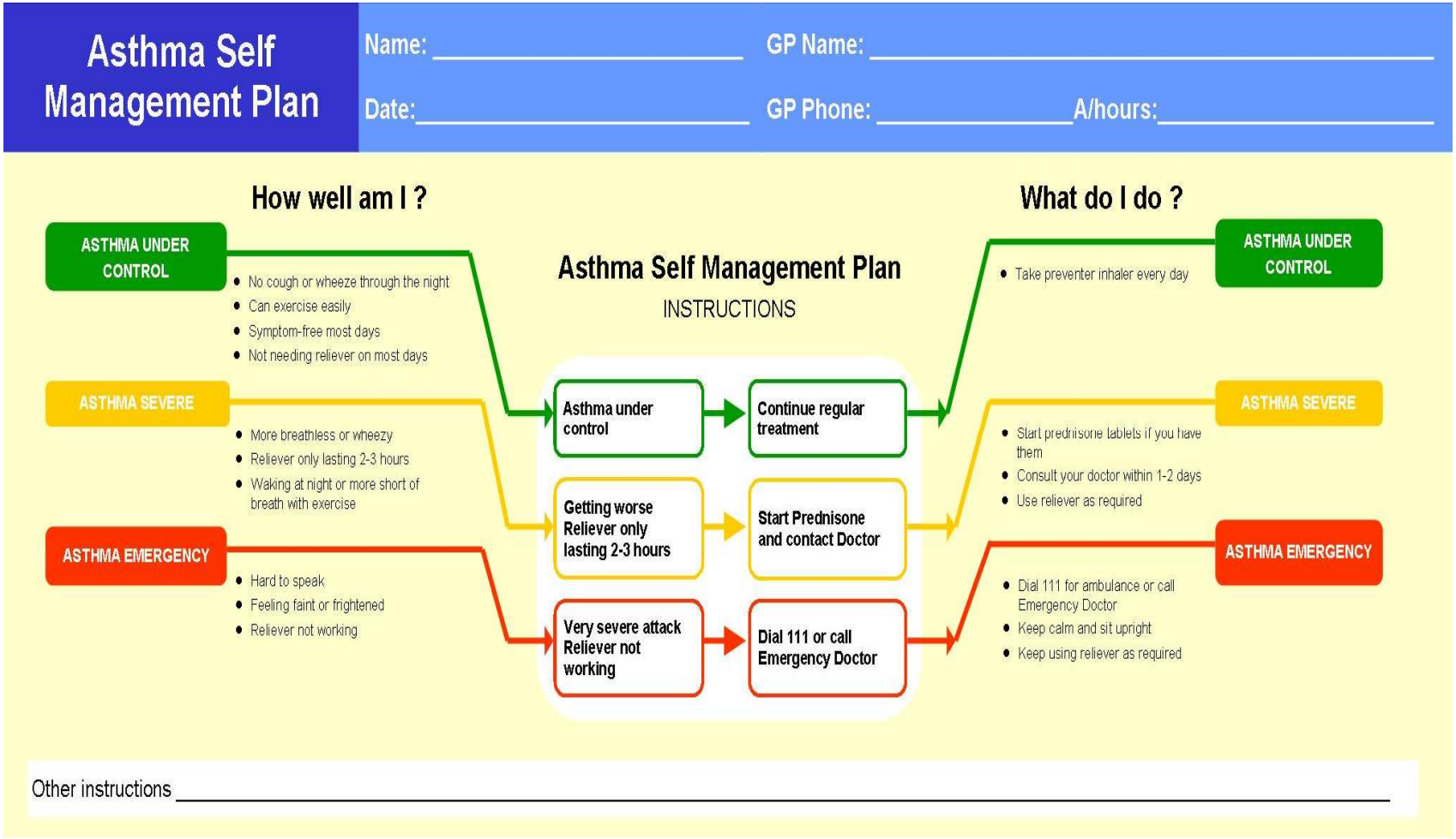


Figure 4.4: Standard Symptoms plan - back

Figure 4.5: Standard Peak flow plan - front

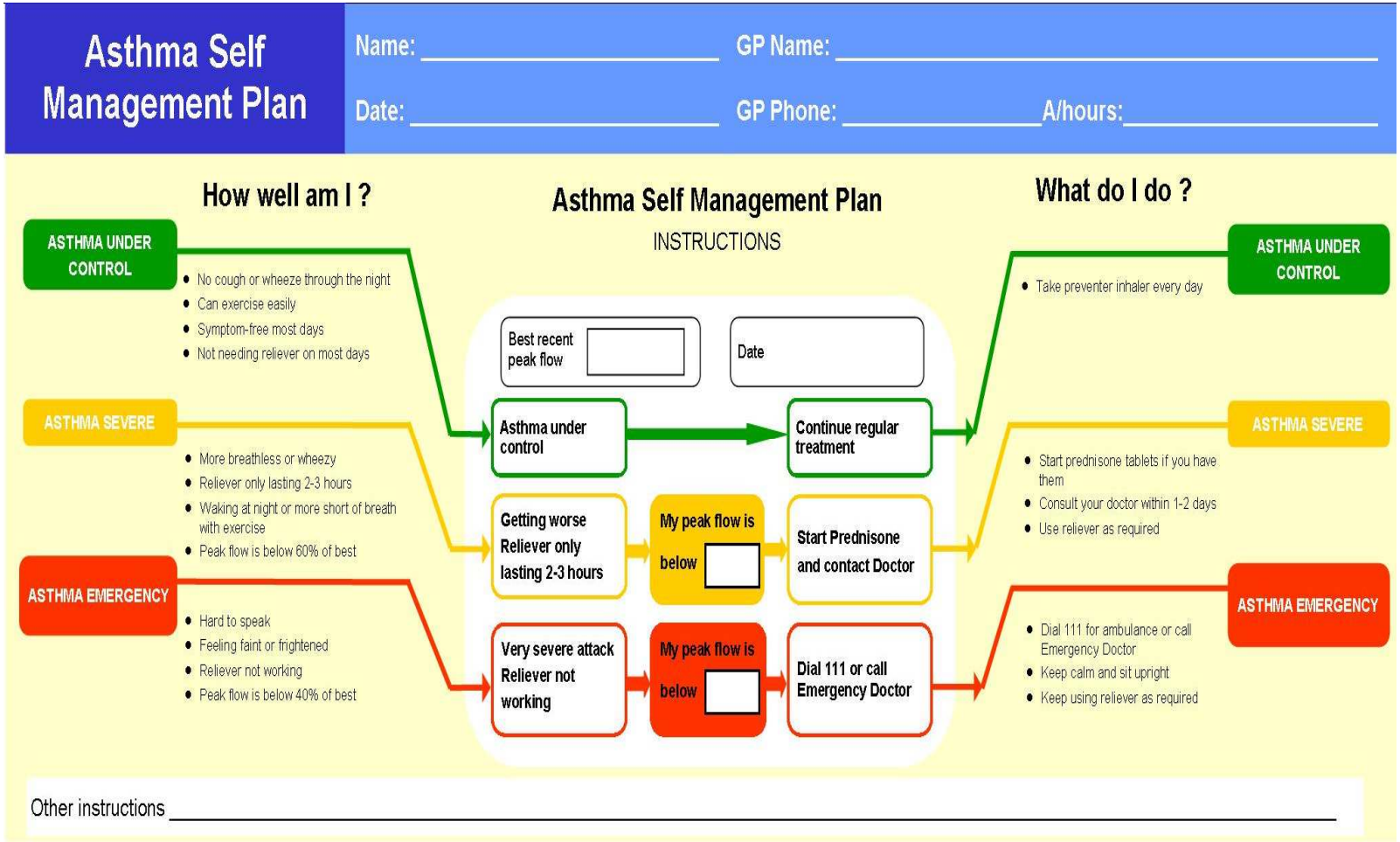


Figure 4.6: Standard Peak flow plan - back

4.9 Asthma Control Questionnaire-7 (ACQ-7)

The ACQ-7 comprised seven questions to give a validated composite score of asthma control (Reddel et al., 2009; Juniper et al., 1999). There were six self-reported questions (relating to asthma symptoms and as-needed beta-agonist use in the preceding one week) and FEV_1 % predicted. Each question was scored on a scale of 0 to 6. The final score was a mean of the seven responses, where 0 represents good control and 6 represents poor control. A score of ≤ 0.75 suggests well-controlled asthma and a score of ≥ 1.5 suggests not well-controlled asthma (Juniper et al., 2006). The minimal clinically important difference is 0.5 (Juniper et al., 2005).

Investigators informed participants on the SMART regimen that their response to Question 6 (as-needed beta-agonist use) should reflect the number of reliever puffs of budesonide/formoterol used (i.e. extra actuations, taken in addition to the four maintenance doses per day). Interpolation was used for ACQ-7 scores where there was one missing value.

4.10 Satisfaction with Asthma Treatment Questionnaire (SATQ)

The SATQ was used to measure patients' satisfaction with their inhaled asthma treatment (Campbell et al., 2003). The questionnaire comprised 26 questions, divided into four domains: effectiveness of medication (eight questions); ease of use

(seven questions); burden of asthma medication (six questions); and side effects and worries (five questions). Each question was scored on a scale of 1 to 7. Negatively phrased questions were reversed for analysis. Domain scores were calculated as the average of the responses for that domain, with higher values indicating greater satisfaction with treatment (range 1 to 7). The total overall score was calculated as the mean of the four domain scores (range 1 to 7). The minimal clinically important difference has not been determined.

4.11 Spirometry

Cardinal Health Micro spirometers (Cardinal Health UK, Kent, UK) were used for lung function measurements. All spirometers passed validation checks of the manufacturer's calibration with a 3 Litre syringe prior to use in the trial and again at the completion of the trial. On-treatment spirometry was performed according to a standardised protocol. Participants were not required to withhold their bronchodilator medication prior to performing spirometry measurements, in order to reflect clinical practice where regular treatment is not usually withheld prior to spirometry (Reddel et al., 2009).

4.12 Medication

Vannair MDIs contained 120 doses per canister and Ventolin MDIs contained 200 doses per canister. The medicine data sheets for Vannair and Ventolin are included in Appendix D.

4.13 Unscheduled medical care for asthma during study participation

If a study participant had an asthma exacerbation during the study, they were advised to contact their GP or visit an ED or after-hours clinic. Participants were aware that they would receive standard medical care (from their GP, after hours or ED) for their asthma during the course of the study.

Patients who had previously kept a course of prednisone at home for emergency use were advised to seek medical review as per their self-management plans whenever a course of prednisone was commenced.

For the three primary care practices, study visits were scheduled separately to usual clinical care. GP-investigators were part of a larger team of physicians at each site. Reception and appointment-booking staff were aware that the participants' medical care (including urgent and unscheduled care for asthma) remained the responsibility of the usual primary care physician.

For the Māori health clinic and hospital site, study visits were scheduled separately to usual clinical care and all medical care remained the responsibility of the participants' primary care physician.

4.14 Pregnancy in female participants

Female patients who were pregnant at baseline were eligible for study participation. Patients who became pregnant during study participation were able to continue trial participation. All pregnancies were reported to the Ethics committee in an expedited manner and data on all pregnancy outcomes were collected and reported to the Ethics committee at trial completion.

4.14.1 Rationale

Current clinical practice allows for the use of combination budesonide/formoterol therapy during pregnancy, as the benefits to both mother and child of adequate asthma control outweigh the theoretical risks of treatment (Schatz and Dombrowski, 2009). The risks and benefits of commencing or continuing with the study were discussed with pregnant patients on an individual basis.

4.15 Visit schedules

Text messages to mobile telephones or telephone calls were made two to three days prior to study visits, in order to confirm attendance. Study visits were scheduled to occur within +/- three days of their due date. If this was not possible, the visit window was extended up to +/- seven days. Patients could also arrange to attend the clinic if they required further inhalers in between study visits. Patients who did not attend their study appointments were contacted by telephone and offered the option of a home or workplace visit.

Participants who withdrew had a recorded date for the cessation of study product (the withdrawal date). Participants were entitled to NZ$20 per visit (£10) for their travel expenses.

4.16 Safety Monitoring

4.16.1 Adverse Events (AEs)

An AE was defined as any untoward medical occurrence in a study participant temporally associated with participation in the trial and the administration of study medication, whether or not considered related to the medicine. An adverse event was therefore any unfavourable and unintended sign, symptom or disease temporally

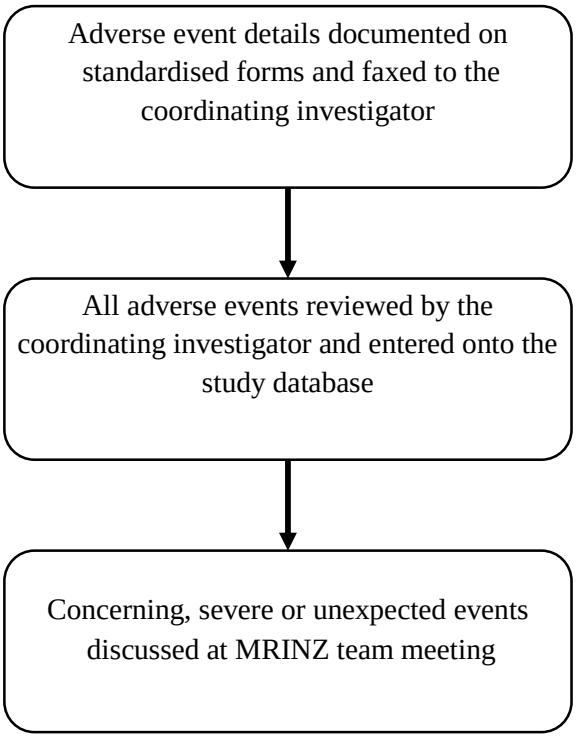
associated with the use of the study treatment. A worsening of a pre-existing medical condition, other than asthma, was considered an adverse event.

AE and SAE data were collected by patient report and from responses to standard questions at study visits:

> 'Have you had any health or medication-related problems since the last visit?'
>
> 'Is there anything new about your health or medication that you wish to discuss?'

Investigators notified adverse events to the coordinating investigator as they occurred, using standardised templates. All adverse events classed as 'severe' or that were unexpected or concerning (as considered by either the investigators reporting the event or the coordinating investigator) were discussed in a team meeting at the MRINZ, which involved the principal investigator (Figure 4.7). Adverse event data were collected and analysed with efficacy data at the end of the study.

Figure 4.7: Process for Adverse Event reporting



4.16.2 Serious Adverse Events (SAEs)

The following events were considered to be SAEs and required expedited reporting to the Ethics committee:

Death;

Life-threatening event;

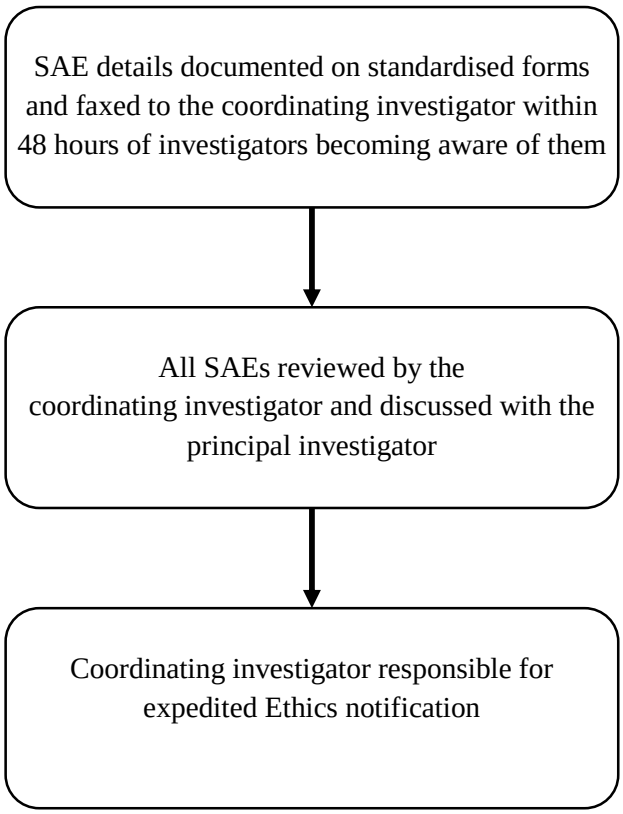
Permanently disabling or incapacitating event;

Hospitalisation or prolongation of hospitalisation [hospitalisation for the purposes of SAE reporting was defined as an admission to hospital and did not include a presentation to the Emergency Department followed by discharge without admission or an admission for elective reasons];

Any event considered serious by the study investigator.

SAEs were notified to the Ethics committee in an expedited manner, usually within 15 days of the investigators becoming aware of them (Figure 4.8). Asthma exacerbations that did not meet the criteria for being considered an SAE were not reported as adverse events, as they were analysed in the efficacy outcomes for the study.

Figure 4.8: Process for Serious Adverse Events reporting



4.16.3 Validation of ED visits and hospital admissions for asthma during study participation

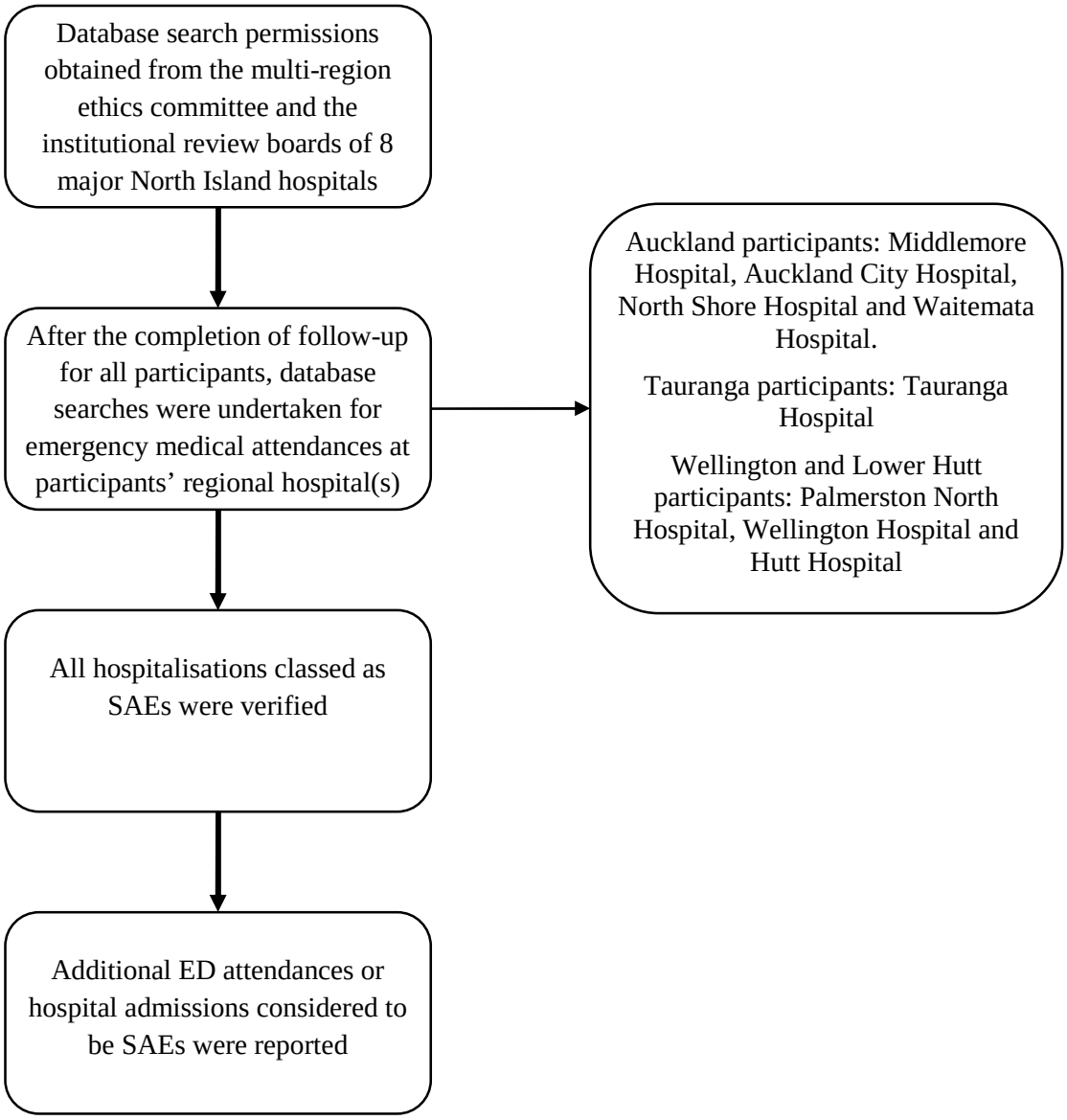
All ED visits and hospital admissions for asthma were verified by searching hospital databases for medical attendances for all participants, from their regional hospital(s) (after the completion of follow-up for all participants). For participants enrolled at the Henderson Medical Centre (Auckland) site, database searches for medical attendances were performed at: Auckland City Hospital; Auckland Middlemore Hospital; Auckland North Shore Hospital; Auckland Waitakere Hospital. For

participants enrolled at CentralMed General Practice (Tauranga) and Papamoa Pines Medical Centre (Tauranga), database searches for medical attendances were performed at: Tauranga Hospital. For participants enrolled at Tu Kotahi Māori Asthma Trust (Lower Hutt), database searches for medical attendances were performed at: Hutt Hospital (Wellington); Palmerston North Hospital (Palmerston North); Wellington Regional Hospital and Keneperu Hospital (Wellington). For participants enrolled at the MRINZ (Wellington), database searches for medical attendances were performed at: Hutt Hospital (Wellington); Palmerston North Hospital (Palmerston North); Wellington Regional Hospital and Keneperu Hospital (Wellington).

4.16.4 Hospital database verification for SAEs at trial completion

The occurrence of all SAEs due to hospitalisation was verified during the hospital database validation process detailed above (Figure 4.9). Any additional SAEs that had not previously been reported were recorded during this process.

Figure 4.9: Hospital database verification for SAEs due to hospitalisation



4.17 Independent Safety Monitoring

An interim safety statistical analysis was conducted by the study statistician, Professor Mark Weatherall, for all unplanned hospitalisations for asthma, once 150 participants had completed the study. This analysis was performed masked to treatment allocation (the results for analysis were provided without the participant identification code, but with the blinded randomised treatment code (e.g. treatment 1 or treatment 2). The results of this analysis were then reviewed by an independent safety monitor. Dr Andrew Brant, Consultant Respiratory Physician & Chief Medical Officer [North Shore Hospital, Waitemata District Health Board, Auckland, New Zealand], who was independent from the study team, acted in this capacity.

The pre-specified interim analysis plan was to compare the proportion of participants with an unplanned hospital admission for asthma with a reference rate of 4.5% using the binomial test for proportions. An exact (Clopper-Pearson) confidence interval was used for the proportion of participants with a hospital admission. The calculated interim p value for performing a safety review of the study (using the ld98 Programme), assuming one interim analysis halfway through the data collection, was 0.006 (using a one sided O'Brien-Fleming bound). If the observed rate exceeded the expected rate with a p value less than 0.006, a safety review of the study was to be undertaken. The p value calculations used the ld98 programme, an alpha spending function, with alpha nominated as 0.05, evenly distributed analysis times, and O'Brien Fleming boundaries. The expected proportion was derived from data from

the Wairarapa Māori asthma project in Te Reo o te Ora (Wairarapa Māori Executive, 1999).

In addition, a comparison of the admission rates as a relative risk of at least one admission using calculated relative risk with asymptotic 95% confidence interval but Fishers exact test was undertaken; and Poisson regression for the relative rate of hospital admissions.

The study statistician was blinded to the treatment groups for this analysis.

If the findings of the safety analysis indicated a safety review was necessary, then termination of the trial was to be considered.

4.18 Primary Outcome Variable

The primary outcome variable was the proportion of participants with at least one high beta-agonist use ('high use') episode during the study. This was defined as the proportion of participants in the SMART group who at any point within the six-month study period used greater than eight actuations of budesonide/formoterol in addition to the four maintenance doses (i.e. equivalent to >12 actuations in total) per 24-hours compared to the proportion of patients in the Standard group who used greater than 16 actuations of salbutamol per 24-hours.

4.18.1 Rationale for Primary Outcome Variable

These high use thresholds were based on the limits of beta-agonist use requiring medical review, defined by the self-management plans (National Asthma Council Australia, 2013; Holt et al., 2004) and supported by the short-term bronchodilator equivalence of 6µg formoterol to 200µg salbutamol with repeat dosing in acute asthma (Balanag et al., 2006; Rubinfeld et al., 2006). In accordance with their self-management plans, participants were advised to seek medical review at these thresholds.

A 24-hour period was defined as 0300 to 0259.

4.18.2 Post-hoc sensitivity analysis

A post-hoc sensitivity analysis was undertaken, using a modified definition of a high use episode for the Standard group, to adjust for the use of budesonide/formoterol in excess of the four maintenance actuations per 24-hours by some participants on occasions.

4.19 Secondary Outcome Variables

These analyses included measures of overuse of beta-agonist therapy, overuse occurring without medical review, underuse of maintenance therapy, asthma control,

lung function, severe exacerbations, ED/hospital attendances and satisfaction with asthma treatment.

4.20 Days of high use

This was defined as the number of days of high use over the six-month study period.

4.21 High use without medical review

This was defined as the number of days of high use without medical review in the following 48-hours, in the sub-group of participants who had at least one high use episode.

4.21.1 Rationale

This 48-hour window was defined as per the Standard self-management plan, which recommends that patients should attend for medical review 'within 1 to 2 days' in the setting of worsening asthma. The SMART plan advises patients to seek medical review on the same day if more than 12 actuations of budesonide/formoterol are taken.

4.22 Marked beta-agonist overuse

This was the proportion of participants and number of days of marked beta-agonist overuse ('marked overuse'). For SMART, this was defined as >12 actuations of budesonide/formoterol in addition to maintenance (i.e. >16 actuations in total) and for Standard, >24 actuations of salbutamol, per 24-hours.

4.22.1 Marked overuse without medical review

This was defined as the number of days of marked overuse without medical review in the following 48-hours, in the sub-group of participants who had at least one marked overuse episode.

4.23 Extreme beta-agonist overuse

This was the proportion of participants and number of days of extreme beta-agonist overuse ('extreme overuse'). For SMART, this was defined as >16 actuations of budesonide/formoterol in addition to maintenance (i.e. >20 actuations in total) and for Standard, >32 actuations of salbutamol, per 24-hours.

4.23.1 Extreme overuse without medical review

This was defined as the number of days of extreme overuse without medical review in the following 48-hours, in the sub-group of participants who had at least one extreme overuse episode.

4.24 Underuse of maintenance budesonide/formoterol treatment

This was the proportion of participants and number of days of underuse of maintenance therapy, defined as zero (non-adherence), ≤1 actuation and ≤2 actuations of budesonide/formoterol per 24-hours.

4.25 Corticosteroid load

4.25.1 ICS dose

This was the mean budesonide dose per day.

4.25.2 Oral corticosteroid dose

This was the oral corticosteroid dose during the study period and the number of courses of oral corticosteroids per year.

4.25.3 Composite corticosteroid load

This was the composite systemic corticosteroid exposure per year, in which the total ICS dose per year, converted to oral prednisone-equivalent dose for systemic effects on adrenal function using the conversion factor of 5000µg inhaled budesonide to 10mg oral prednisone determined in a previous bioequivalence study (Aaronson et al., 1998), was added to the oral corticosteroid dose per year.

4.26 Severe asthma exacerbations

This was the risk and the rate of severe asthma exacerbations and the time to first severe asthma exacerbation.

4.26.1 Definition of severe asthma exacerbations

A severe asthma exacerbation was defined as the use of systemic corticosteroids (tablets, suspension or injection), or an increase from a stable maintenance dose (for patients commenced on prednisone after commencement of the study), for at least three days or a hospitalisation or ED visit because of asthma, requiring systemic corticosteroids. Courses separated by seven days or more from the completion of the preceding course were classed as separate severe exacerbations (Reddel et al., 2009).

4.27 ED visits and hospital admissions for asthma

This was the risk and rate of hospital attendance (ED visits and/or hospital admission) and hospital admission for asthma.

4.28 Asthma control

This was measured by ACQ-7 score.

4.29 Lung function

This was measured by on-treatment FEV_1.

4.30 Satisfaction with inhaled asthma therapy

This was measured by SATQ score.

4.31 AEs

This was recorded as AEs occurring in study participants.

4.32 SAEs

This was recorded as SAEs occurring in study participants.

4.33 Dose dumping

The pre-specified plan was to remove electronic medication use data on the day of study visits prior to analysis, because dose dumping may occur at this time (Rand et al., 1992).

4.33.1 Database searches for the occurrence of possible dose dumping

There is no consensus definition for dose dumping. However, the electronic medication use database, with and without medication use data from study visit days included, was searched post-hoc for patterns of use which might be consistent with dose dumping, in order to quantify the occurrence of these events in the dataset. The definition of dose dumping used was:

> ≥100 actuations within three hours [as per a definition used previously (Rand et al., 1992)].

For the SMART group, data descriptions summarised the occurrence of possible dose dumping with budesonide/formoterol inhalers. For the Standard group, data descriptions summarised the occurrence of possible dose dumping with salbutamol inhalers.

4.34 Statistical methods

Analysis was by intention-to-treat. SAS version 9.2 was used.

4.34.1 Treatment exposure time

This was defined as the number of days from the Visit 1 date to the date of cessation of the study product (the last recorded study visit or the withdrawal date).

For analyses relating to electronic medication use data, the number of study visit days undertaken (one to five) was subtracted from the treatment exposure time, as electronic medication use data on the day of study visits was removed from the analysis.

4.34.2 Period of observation ('follow-up time')

This was defined as the number of days from Visit 1 to the last recorded study visit (for both completed and withdrawn participants).

4.34.3 Statistical methods for the overuse (high use, marked overuse and extreme overuse) analyses

Analysis of the number of participants with at least one episode of overuse was by calculation of relative risk with appropriate confidence intervals. Analysis of the relative rates of overuse, i.e. the number of days with an overuse episode per days of treatment exposure, was by Poisson regression with an offset for the treatment exposure. The analysis suggested over-dispersion and a dispersion term was used to adjust for over-dispersion.

4.34.4 Sensitivity analysis for the primary outcome variable

This post-hoc analysis was undertaken following the observation that 143 participants in the Standard group used in excess of their four maintenance actuations of budesonide/formoterol on at least one day during their exposure to treatment. A modified definition of 'high beta-agonist use' for the Standard group was utilised for this analysis by converting budesonide/formoterol actuations in excess of the four maintenance actuations to bronchodilator equivalent doses of salbutamol, using the conversion of 6µg of formoterol (one actuation) to 200µg of salbutamol (two actuations). The formula below was used, whereby a high use episode was defined as follows:

High use: [(n-4) x 2] + number of salbutamol actuations, is greater than 16, per 24-hour period, where n is the number of budesonide/formoterol actuations taken, 4 represents the prescribed maintenance budesonide/formoterol doses and the value 2

is the bronchodilator equivalence conversion factor of 1:2 for budesonide/formoterol to salbutamol.

4.34.5 Statistical methods for the overuse without medical review analyses

These analyses were undertaken in the subgroup of participants who had an overuse episode (high use, marked overuse or extreme overuse). The number of days of overuse without medical review and the adjusted treatment exposure days for the calculation of rates was determined using the following rules.

For every overuse day (the 'index day'), the database was checked to determine if the patient attended for medical review (primary care clinic, after-hours clinic or hospital) either on the day of overuse or the next day. This 48-hour window was defined as per the Standard self-management plan, which specifies that the patient should attend for medical review 'within 1 to 2 days' in the setting of worsening asthma. The SMART plan advises patients to seek medical review on the same day if more than 12 actuations of budesonide/formoterol are taken.

If the participant attended for medical review, then overuse occurring on the index day, the day of medical review and in the seven days after medical review was not counted as overuse (the 'stand-down' period). In effect, overuse occurring on these days was 'permissible' as the patient had attended for medical review in the setting of this exacerbation. If the patient attended for repeated medical reviews during the stand-down period, then the seven-day period where overuse without medical review was not counted was restarted.

These definitions applied to this outcome variable only and were chosen as ATS/ERS definitions of exacerbations requiring prednisone separate exacerbations by seven days (Reddel et al., 2009). The stand-down period was extended using the rules above in the setting of repeated medical visits as the purpose of this analysis was to explore the relationship between the 'index' overuse episode and the first episode of medical review following this.

An adjusted treatment exposure was calculated by subtracting the number of stand-down days from the overall treatment exposure for the participant.

Analysis of the relative rates of overuse without medical review, i.e. the number of days with an overuse episode without medical review per adjusted treatment exposure days, was by Poisson regression with an offset for the adjusted days of treatment exposure. The analysis suggested over-dispersion and a dispersion term was used to adjust for over-dispersion.

4.34.6 Statistical methods for the underuse variables

Relative risk and appropriate confidence intervals were calculated for the number of participants with at least one event (days with zero actuations, ≤1 actuation and ≤2 actuations of budesonide/formoterol per 24-hours). Relative rates of days of underuse were calculated by Poisson regression with an offset of the logarithm of the time of exposure. The variables of days of underuse were over-dispersed and a deviance-based over-dispersion correction term was used in Poisson regression.

4.34.7 Statistical methods for severe exacerbations and hospital attendances

Relative risk and appropriate confidence intervals were calculated for the number of participants with at least one event (severe exacerbation, hospital admission, ED visits, at least one course of corticosteroids). Relative rates were calculated by Poisson regression with an offset of the logarithm of the period of observation (severe exacerbations, hospital admissions, ED visits, number of courses of corticosteroids).

For hospital attendances where only a one-off dose of IV hydrocortisone was given, this was counted as a one-day course of prednisone using the conversion 100 mg hydrocortisone = 25mg of prednisone. For hospital attendances where IV hydrocortisone was given in addition to oral prednisone, this dose was converted to prednisone as above and added to the total prednisone exposure for that exacerbation.

Survival analysis was with a Kaplan-Meier plot and Cox Proportional Hazards calculation for the time to first severe exacerbation. The proportionality assumptions was tested by fitting an interaction term between treatment and time to first severe exacerbation; this was not statistically significant (p=0.52) (Collett, 2003). Neither treatment group had 50% reaching a first severe exacerbation; therefore, a median time-to-event could not be calculated.

4.34.8 Statistical methods for mean ICS dose/day analysis

ICS use had a skew distribution which was converted to a symmetric distribution with the natural logarithm transformation. For this calculation, the unit of time was

the treatment exposure time and the analysis was by converting to ICS use per year (annualised ICS use). The logarithm of the annualised ICS use was the response variable in a weighted normal linear model with the randomised treatment as a predictor and the treatment exposure time as a weight so that individuals with longer periods of treatment exposure were given more weight and those with shorter periods of observation less weight in the analysis.

The exponent of the difference in logarithms, SMART minus Standard, is interpreted as the ratio of mean values of annualised ICS use, although the ratio of mean values applies to any unit of time e.g. days or years.

4.34.9 Statistical methods for oral corticosteroid dose analysis

The pre-specified analysis for the continuous variables that did not meet normal distribution assumptions, with or without transformation, was the non-parametric Mann-Whitney test. There was no prednisone use at all for 80% of the SMART group and 66% of the Standard group. Analysis with the Mann-Whitney method was problematic because a large number of participants had no oral corticosteroid use. A more meaningful way of examining the difference in prednisone use between groups, categorisation into prednisone bands of use, was undertaken.

Chi-square tests for contingency tables derived from the corticosteroid exposure measurements were used for oral corticosteroid use. Bands for oral corticosteroid dose for the contingency table were (mg prednisone): 0; 0 to 200; 200 to 400; 400+.

4.34.10 Statistical methods for the composite systemic corticosteroid exposure per year analysis

The total ICS dose/year, converted to oral prednisone-equivalent dose for systemic effects on adrenal function using the conversion factor of 5000µg inhaled budesonide to 10mg oral prednisone determined in a previous bioequivalence study (Aaronson et al., 1998), was added to the oral corticosteroid dose/year. The unit of time was the total observation time (follow-up time).

The analysis of composite systemic corticosteroid exposure was calculated by converting to prednisone dose per year (annualised prednisone dose).

Composite systemic corticosteroid exposure had a skew distribution which was converted to a symmetric distribution with the natural logarithm transformation.

The logarithm of the annualised prednisone dose was the response variable in a weighted normal linear model with the randomised treatment as a predictor and the period of observation as a weight so that individuals with longer periods of observation were given more weight and those with shorter periods of observation less weight in the analysis.

The exponent of the difference in logarithms, SMART minus Standard, is interpreted as the ratio of mean values of annualised composite systemic corticosteroid exposure, although the ratio of mean values applies to any unit of time e.g. days or years.

4.34.11 Sensitivity analysis with one participant in the Standard group removed from the analyses of oral corticosteroid dose and composite systemic corticosteroid exposure

One Standard participant self-administered an overdose of 800mg prednisone per day for five days for asthma. Sensitivity analyses, performed with this one participant in the Standard group with an overdose of prednisone removed from the dataset, were performed for oral corticosteroid dose and composite systemic corticosteroid exposure.

4.34.12 Statistical methods for the asthma control and lung function analyses

The pre-specified analysis method was a mixed linear model examining response profiles at each time point using random effects for individual subjects and an unstructured covariance pattern to account for correlation between measurements on the same subjects. As suggested (Fitzmaurice, Laird and Ware, 2004), the model forces a common intercept and adjusts for baseline values in this way.

FEV_1 % predicted values were calculated using the ECSC reference equations (Miller et al., 2005).

4.34.13 Statistical methods for the SATQ analysis

Comparisons were performed by ANCOVA with the Visit 1 value as a baseline covariate, to provide an adjusted treatment difference between the groups.

4.34.14 Baseline data for study participants

Statistical comparisons of baseline characteristics between groups were not performed for the following reasons, as per CONSORT guidelines (Schulz, Altman and Moher, 2010). Firstly, there is generally a lack of power to detect clinically important differences in the variables at baseline, as the study is powered to detect a difference in the primary outcome not in baseline variables. Secondly, undertaking baseline comparisons inflates the overall study type I error rate. Thirdly, it is unclear what hypothesis is being tested if statistical comparisons of baseline characteristics are performed e.g. are they to determine whether randomisation has 'worked'.

4.34.15 Exploratory post-hoc analyses

The following analyses were post-hoc: the sensitivity analysis for the primary outcome variable; overuse without healthcare review in the participants with marked and extreme overuse; underuse defined as zero (non-adherence), and ≤2 actuations of budesonide/formoterol per 24-hours; and, oral corticosteroid dose by contingency tables.

4.35 Power and sample size

The actual use of beta-agonists in the context of an asthma exacerbation has not been defined and prior studies have shown variable rates of asthma exacerbations in patients.

In the RELIEF study (Pauwels et al., 2003b), 43% of the patients with Stage 4 asthma severity had at least one exacerbation over a six-month period. A pooled analysis of studies in moderate to severe asthma patients showed an exacerbation rate of 1.5 per year in the control group (Bousquet et al., 2005). One of the primary SMART studies reported that 22% of patients with a recent severe exacerbation and who were receiving maintenance fixed-dose budesonide/formoterol and as-needed terbutaline experienced a severe exacerbation over a 12-month period (Rabe et al., 2006a). Thus, for the purposes of this study, we predicted that approximately 40% of asthma patients might have a severe exacerbation (defined as requiring systemic corticosteroids) over a six-month period.

A prior NZ study showed that 85% of patients admitted to hospital with asthma exacerbations reported using ≥16 actuations of SABA in the 24-hours prior to admission (Windom et al., 1990a). There is, however, uncertainty as to the actual use of beta-agonists in the context of a severe asthma exacerbation not requiring hospital admission. Also, it is not certain what proportion of patients use greater than 16 inhalations of salbutamol and are not prescribed oral corticosteroid therapy and thus do not meet the severe exacerbation definition used above.

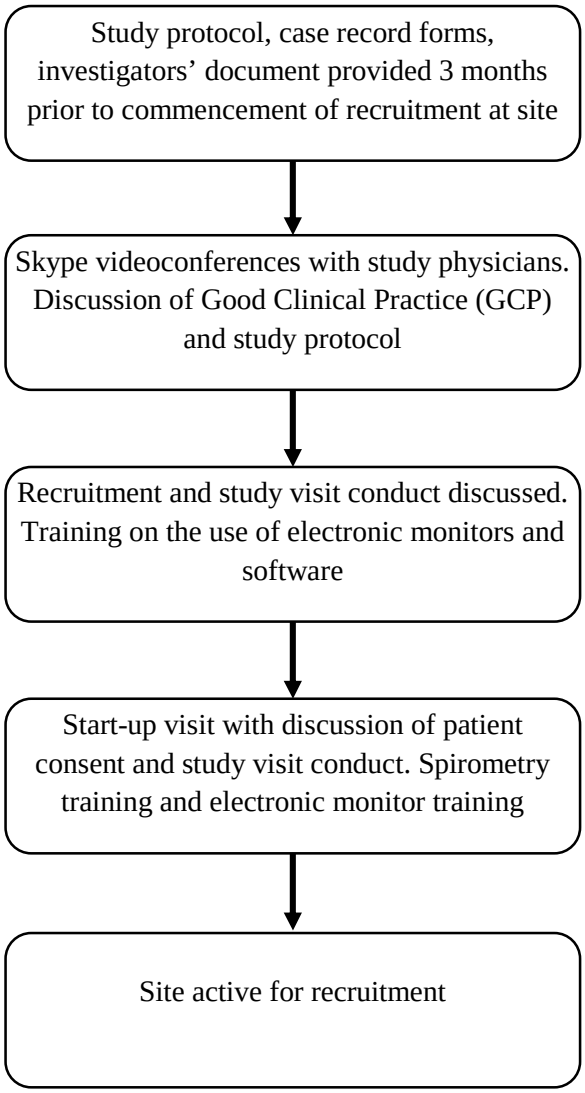
We assumed that half of patients would have an episode of high use in the setting of a severe exacerbation (20% of the control group) and an additional 20% of the remaining 80% of patients would have an episode of high beta-agonist use (16% of the control group); thus, approximately 36% of asthma patients were expected to have a high beta-agonist use episode over six months in the Standard group.

If 300 individuals were recruited, it was predicted that approximately 108 patients would have a high use episode over the course of the study. 150 patients in each treatment arm had 80% power ($\alpha = 0.05$ in a two-sided test) to detect a high beta-agonist use rate of 21.4%, an absolute reduction of approximately 15%, a relative risk of just under 0.6.

4.36 Study sites setup

The process for distant study site set-up [Auckland and Tauranga sites] is summarised in Figure 4.10. For the Tu Kotahi Māori Asthma Trust site, comparable training was provided in person.

Figure 4.10: Study site set-up



4.36.1 Pre-startup training

Training in good clinical research practice, the study protocol and study processes, and use of electronic monitoring was undertaken via Skype video conference in the three months prior to start-up. All investigators were provided with a detailed Investigators' document. Study oversight was provided by the clinical coordinating investigator.

4.36.2 Start-up site visit

A start-up site visit was performed, including training in the use of electronic monitoring and spirometry. All sites were provided with standardised case record forms on 'no carbon required' duplicate paper. For Tu Kotahi Māori Asthma Trust site, study visits were jointly performed by Mitesh Patel and a study nurse.

4.36.3 Within-trial updates

Regular study newsletters were used to keep all investigators informed of current study progress and key protocol issues.

4.37 Trial monitoring procedures

Trial data monitoring was performed both by on-site visits and off-site (remote) data checking.

4.37.1 Site visits

Sites had within-trial and close-out visits, undertaken by Mitesh Patel. At site visits, randomisation logs, study box logs, informed consent forms and spare monitor logs were inspected.

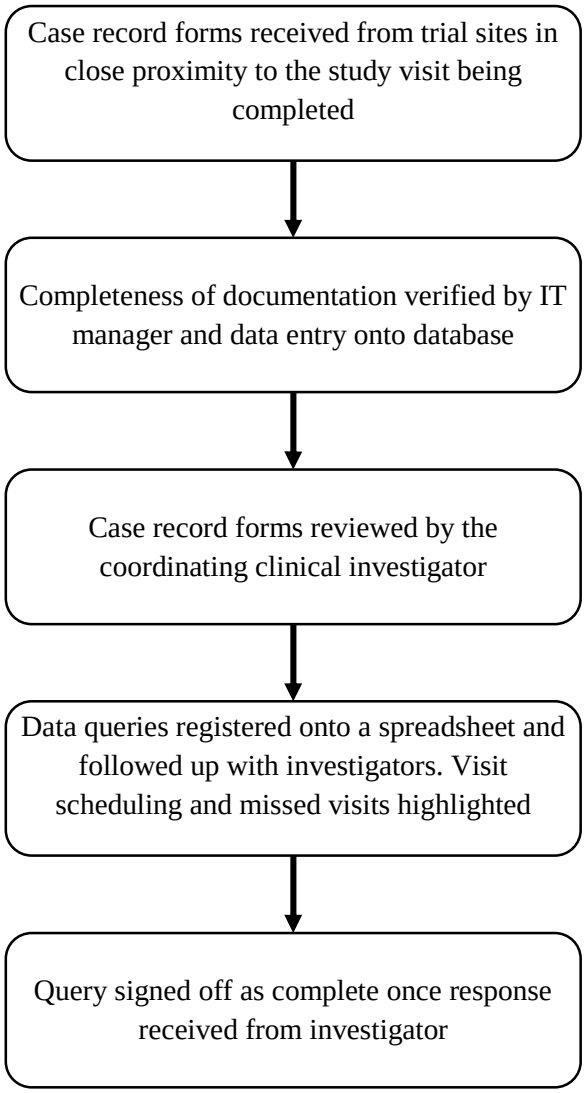
4.37.2 Remote data checking

All sites were responsible for faxing copies of randomisation logs, study box logs and use of spare monitor logs at regular intervals to the MRINZ.

Sites were required to courier case record forms to the MRINZ as soon as practicable after study visits. Case record forms were completed on self-duplicating paper, allowing one copy to remain with the trial site. On receipt of visit documentation at the coordinating trial site, a standardised protocol was followed whereby database entry and data completeness checks were performed by an IT manager, together with review of all CRFs by Mitesh Patel (Figure 4.11). All CRFs were double-checked for completeness in this manner, in close proximity to the study visit. Data queries were recorded and subsequently followed up with investigators until resolution.

Tracking of visit scheduling was also performed using this process in order to identify participants who had missed study visits and who required further follow-up contact.

Figure 4.11: Process for data monitoring for remote study sites



4.38 Database checks at study completion

4.38.1 Clinic recorded measurements

After study completion, database queries were performed to identify erroneous, outlying or missing data for clinic recorded measurements such as FEV_1, ACQ-7 and SATQ. Database entries for baseline characteristics such as asthma medication use, smoking history and pre-study exacerbation data were checked for completeness.

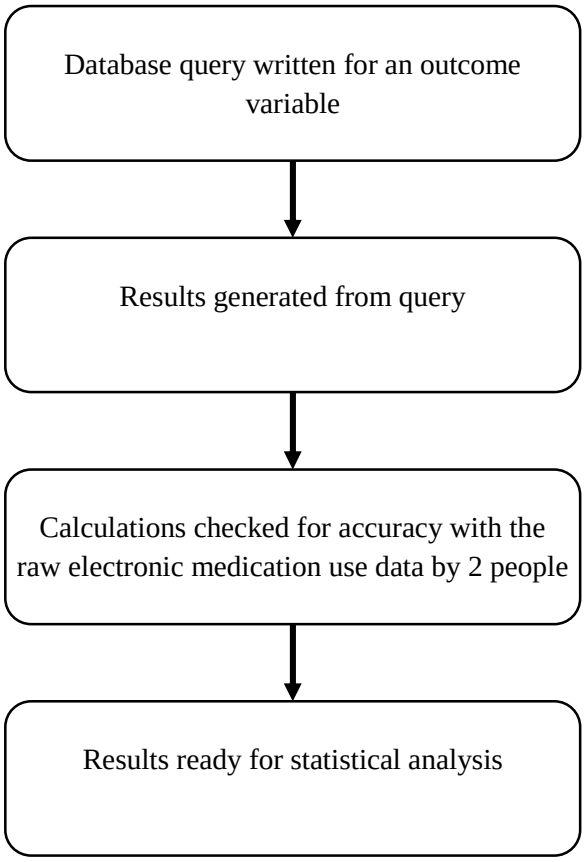
The following data were double data entered: all doses, durations and dates of corticosteroid courses for asthma occurring during study participation; dates of attendance at GP clinics or ED for worsening asthma during study participation; and, ACQ-7 scores.

4.38.2 Electronic medication use data

Data on loss of inhalers and use of non-study inhalers was collected prospectively as described previously.

A specialist database engineer [Craig Boyd, BoydHQ Limited] 'custom-designed' the electronic medication database and built the relationships between inhaler actuation data from participant use of MDIs and clinical outcomes, such as severe asthma exacerbations. Database programmes were written to generate data queries to provide results for statistical analysis (Figure 4.12).

Figure 4.12: Process for database queries and checks for study outcomes



Database calculations for study outcome variables were double-checked for accuracy with a sample of the raw data by two people prior to statistical analysis.

4.39 Standards for asthma clinical trials

The ATS/ERS statement on standardising endpoints for asthma clinical trials (Reddel et al., 2009) provides detailed guidance on the design of trials, choice of outcome variables, measurement techniques, data analysis and trial reporting. This was supplemented in 2012 by guidelines relating to the assessment of asthma outcomes in clinical trials (Busse et al., 2012). The trial protocol was designed in line with the 2009 ATS/ERS statement and subsequent data analysis and trial reporting followed the guidance set out in both of the above documents.

Trial reporting adhered to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines (Moher et al., 2010; Schulz et al., 2010) and extended guidelines for pragmatic design RCTs (Zwarenstein et al., 2008) and RCTs reporting on treatment harms (Ioannidis et al., 2004) (Appendix E).

4.40 Ethics

All investigators were trained in Good Clinical Practice Guidelines as per the International Conference on Harmonisation of Technical Requirements for

Registration of Pharmaceuticals for Human Use (ICH Harmonised Tripartite Guideline, 1996). The study received full approval by the New Zealand Multi-Region Ethics Committee (Reference MEC/09/11/127) on 12 May 2010 (Appendix F) and was conducted according to the New Zealand Health and Disability Ethics Committee's standards of clinical trial conduct (National Ethics Advisory Committee, 2012). Participants were provided a detailed information sheet (Appendix B) and discussed the study with a physician prior to enrolment. All participants provided written informed consent prior to any study-specific procedures.

The trial was registered with the Australian New Zealand Clinical Trials Registry on 22 June 2010 (Appendix G), number ACTRN12610000515099.

4.41 Funding

The study was fully funded by the Health Research Council of New Zealand, a government funding organisation. The funding source had no involvement in the study design; collection, analysis and interpretation of data; or preparation of any written reports.

Chapter Five: Electronic monitor setup, software and website functions

5.1 Aims

The aims of this chapter are:

1. To describe the pre-study electronic monitor checking protocol that was performed in the SMART study RCT.
2. To detail the process of electronic monitor setup and organisation at the coordinating trial site.
3. To describe the within-trial electronic monitor and data checking protocols.
4. To detail the flow of monitors in the trial from randomisation to study completion.
5. To describe the functions of the software that was used to access data stored on the electronic monitors.
6. To detail the functions of the website database that was utilised in the SMART study RCT.

5.2 Pre-study monitor check protocol

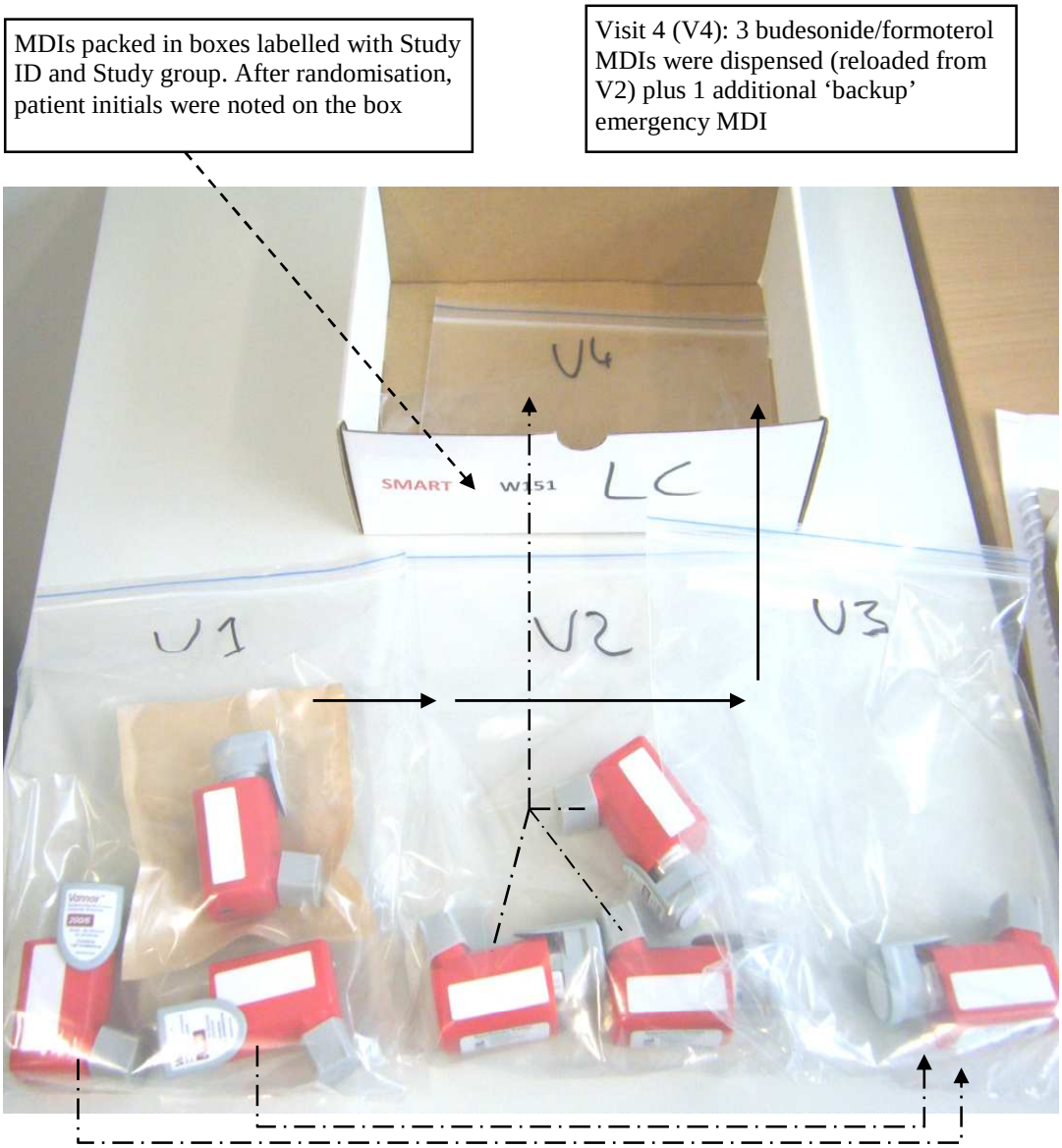
All monitors were loaded with study medication canisters and tested at the coordinating trial site using the following protocol prior to patient use (pre-study use

checks). The MDI (i.e. the monitor loaded with a medication canister) was firstly reset by connecting to a computer via a USB connection and using dedicated software (this cleared the monitor memory and synchronised the monitor clock to the computer clock). Two actuations were performed and recorded on a paper diary. A further two actuations were then performed at least two hours later. The number, date and time of the four actuations, as well as the unique monitor identification number, were then checked for accuracy by comparing the data stored on the monitor to the paper diary. MDIs that were 100% accurate were reset and ready for packaging for use as described below. Any MDIs that failed this pre-study check were removed from circulation and returned to the manufacturer for further fault analysis. Testing was undertaken by one of two trained investigators (Mitesh Patel and Janine Pilcher) under standardised conditions.

5.3 MDI packaging for trial use

MDIs passing the pre-study checks were packaged at the coordinating trial site into boxes labelled with the Participant identification (ID) code and either ‘SMART’ or ‘Standard’ (Figure 5.1 and Figure 5.2). A spreadsheet was used to track all MDIs that were packaged into boxes.

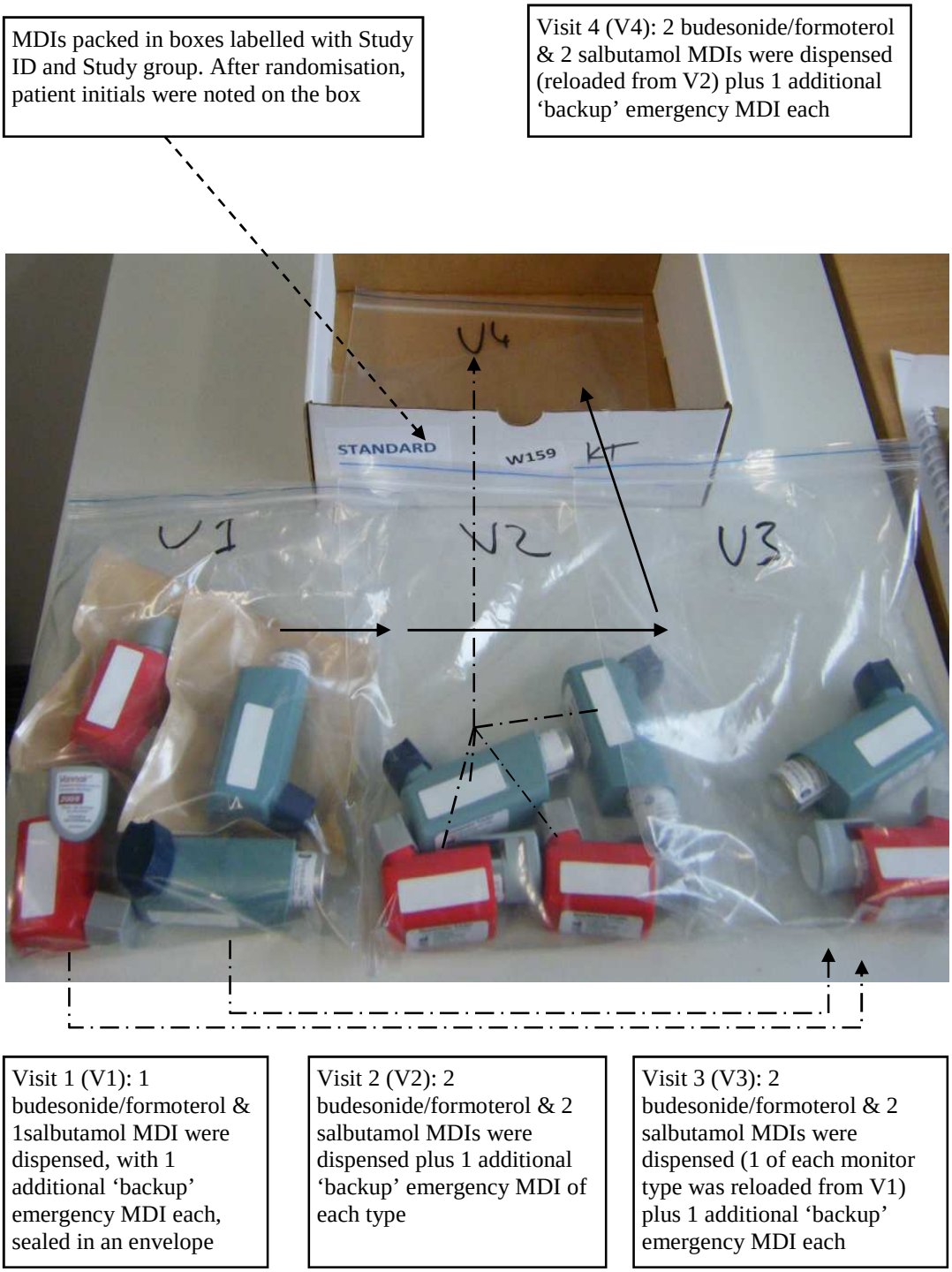
Figure 5.1: SMART group MDI packaging and monitor flow



Denotes reuse of monitors between visits (with reloading of medication canister)

Denotes transfer of (unused) emergency MDI between visits

Figure 5.2: Standard group MDI packaging and monitor flow



5.4 Coordinating trial site checks of monitor packaging

After packaging into boxes, the accuracy of the spreadsheet tracking log and the website database were verified by an investigator independent of the team undertaking study visits. The MDIs packaged in the boxes were checked with the spreadsheet log. The spreadsheet log was, in turn, used to verify that the monitors allocated to a Participant ID on the website were correct (Figure 5.3). In this way, every monitor was correctly accounted for and traceable both on the spreadsheet log and the website database. Each site was then provided with a supply of SMART and Standard boxes ready for use. A separate stock of replacement monitors was also available to each trial site to substitute for lost, damaged or malfunctioning monitors.

5.5 Monitor flow in the SMART study RCT

After gaining informed consent and confirming eligibility, participants were randomly allocated to the SMART or Standard treatment groups. Investigators selected the next unused box (by group) from their stock of study boxes (Figure 5.4). The code on the box determined the Participant ID. The box was annotated with the patient's initials to signify that it was now 'active' in the trial. This process of allocation of study boxes is summarised in Figure 5.5.

Figure 5.3: Coordinating trial site MDI packaging verification process

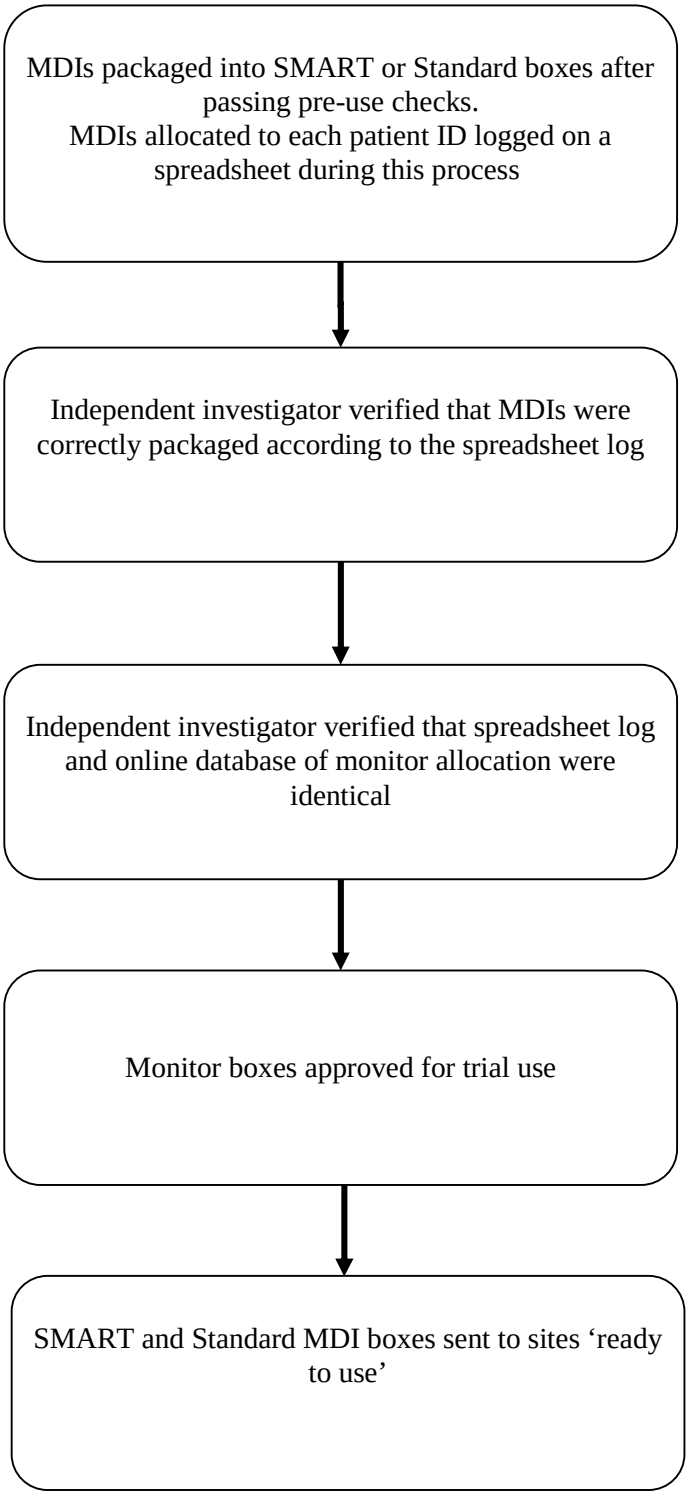
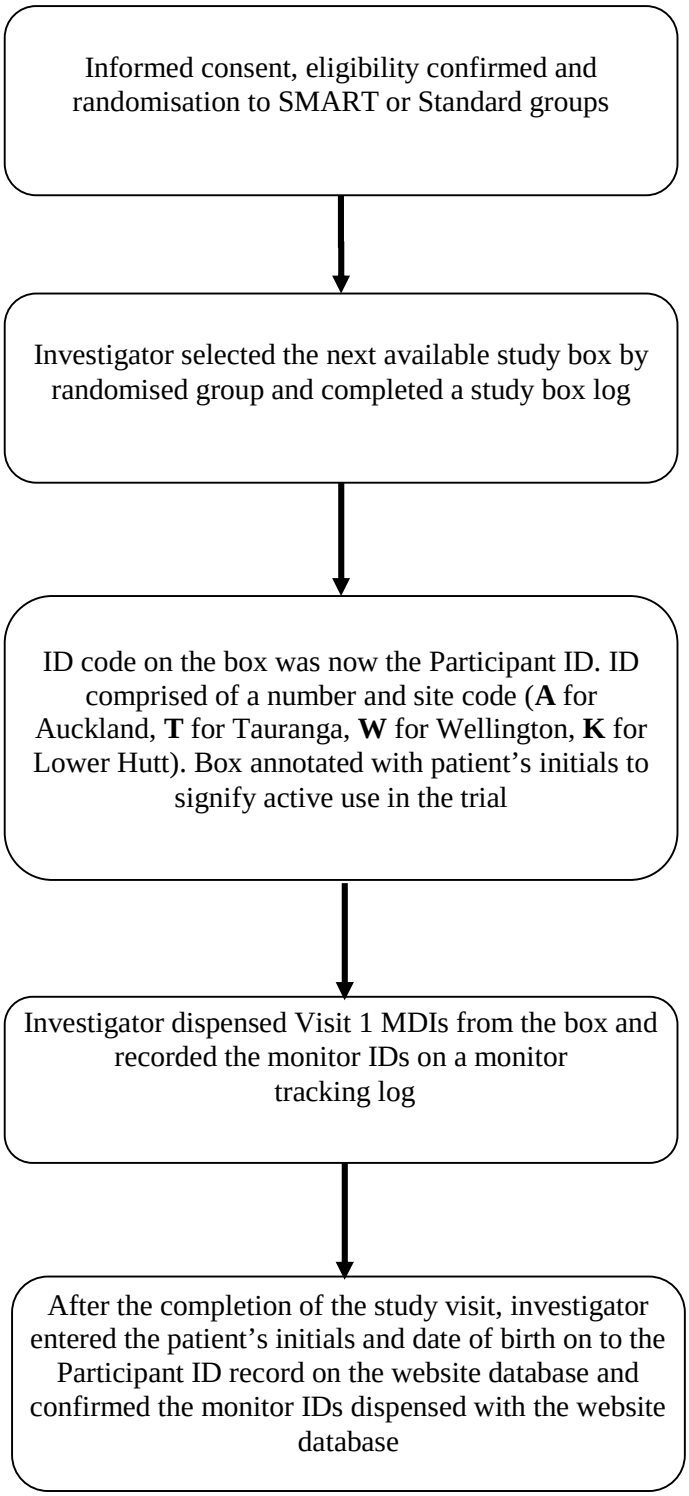


Figure 5.4: Study boxes supplied to sites

Figure 5.5: Allocation of study boxes after randomisation



5.5.1 Flow of MDIs for participants randomised to the SMART group

For the SMART group, two budesonide/formoterol MDIs were provided for the initial three-week long study window (Figure 5.1). One further budesonide/formoterol MDI was provided in a sealed envelope, as the emergency 'backup' inhaler (Figure 5.1). Each monitor had a unique ID number; investigators documented these monitor IDs on a paper tracking log at the time of dispensing.

At study Visits 2 to 4, all the previously dispensed MDIs were collected from participants and were set aside for upload after the study visit. The monitor ID numbers were recorded on the paper tracking log. Three budesonide/formoterol MDIs were then provided for seven-week long study windows (Figure 5.1). The emergency backup inhaler was re-issued to participants at study Visits 2 to 4, provided it remained unused (Figure 5.1). If used by participants, it was replaced with a new budesonide/formoterol MDI.

After the study visit was completed, data upload was performed from all the collected MDIs. The plastic monitor casings were reused so that following data upload, new medication canisters were inserted into the monitors, in preparation for dispensing at the next visit. Thus, monitors that were dispensed at Visit 1 were collected at Visit 2, and dispensed again at Visit 3 (Figure 5.1). Monitors that were dispensed at Visit 2 were collected at Visit 3 and dispensed again at Visit 4 (Figure 5.1).

Each SMART participant had a minimum allocation of seven budesonide/formoterol monitors for the 24-week trial period. Monitors remained patient-specific during the trial.

5.5.2 Flow of MDIs for participants randomised to the Standard group

For the Standard group, one budesonide/formoterol and one salbutamol MDI were provided for the initial three-week long study window (Figure 5.2). One further budesonide/formoterol and salbutamol MDI each were also provided in sealed envelopes, as emergency 'backup' inhalers (Figure 5.2). As previously, monitor ID numbers were logged on a paper tracking log on dispensing and collection of MDIs at study visits.

At study Visits 2 to 4, all the previously dispensed MDIs were collected from participants and were set aside for upload after the study visit. Two budesonide/formoterol and two salbutamol MDIs were provided for seven-week long study windows (Figure 5.2). The emergency backup inhalers were re-issued to participants at study Visits 2 to 4, provided they remained unused (Figure 5.2). If used by participants, they were replaced with a new budesonide/formoterol or salbutamol MDI.

After the study visit was completed, data upload was performed from all the collected MDIs. The plastic monitor casings were reused so that following data upload, new medication canisters were inserted into the monitors, in preparation for dispensing at the next visit. Thus, monitors that were dispensed at Visit 1 were collected at Visit 2, and dispensed again at Visit 3 (Figure 5.2). Monitors that were

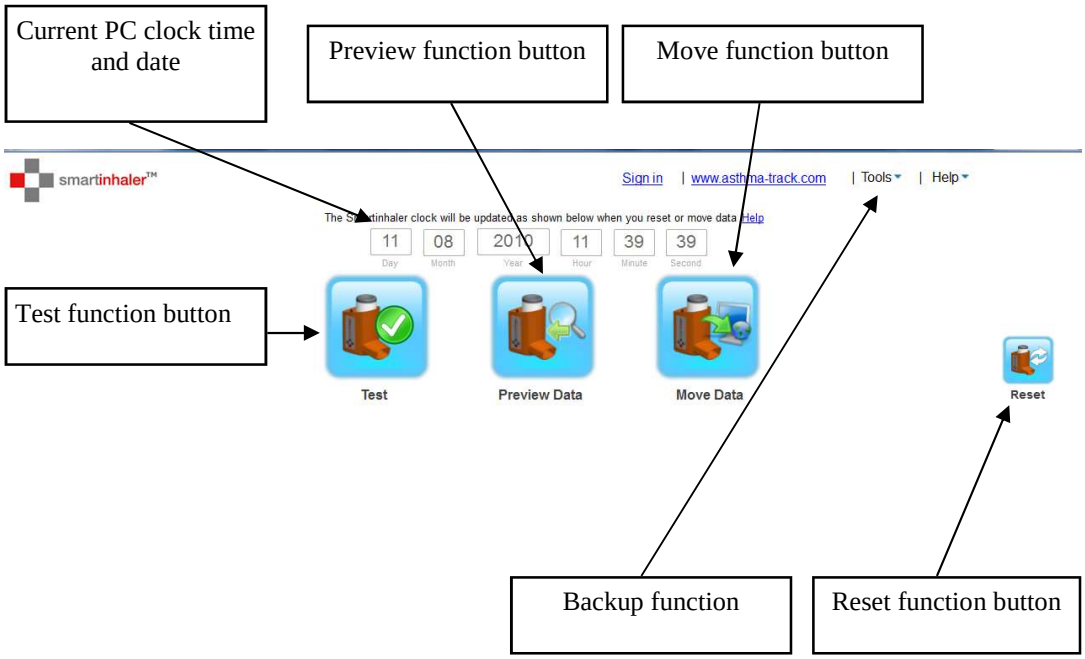
dispensed at Visit 2 were collected at Visit 3 and dispensed again at Visit 4 (Figure 5.2). Each Standard participant therefore had a minimum allocation of five budesonide/formoterol monitors and five salbutamol monitors for the 24-week trial period. Monitors remained patient-specific during the trial.

5.6 Computer software development for the trial

From February 2010 to June 2010, customised software (Connection Centre, Nexus6 Limited, Auckland, New Zealand) for the management of data from the electronic monitors was developed. This involved collaboration with a software engineer at Nexus6 Limited, who tailored the software according to the requirements for the trial. An online, website-based database was also created for the trial. The key elements of the software and online database are described below.

The software allowed investigators to perform five key functions: ‘Preview’; ‘Move’; ‘Backup’; ‘Test’; and ‘Reset’ (Figure 5.6). These will be discussed in turn.

Figure 5.6: Software home page



5.6.1 Software 'Preview' function

Preview allowed investigators to view data stored on the electronic monitor on their personal computer (PC). Investigators were firstly required to check that the date and time set on their PC was correct, as the monitor clock was synchronised to the PC clock. A monitor could then be connected to the PC using a USB computer connection. By selecting the 'Preview' button, data on the monitor was displayed in numerical and graphical format (Figure 5.7). This allowed investigators to verify that data was present on the monitor, prior to transfer to the online database. Monitor ID, PC clock, internet connectivity and monitor battery charge were also displayed (Figure 5.7).

5.6.2 Software 'Move' function

The Move function allowed data stored on the monitor to be transferred to the website database. On selecting the Move button, computerised processes occurred in sequence to simultaneously check the monitor clock, backup stored data to the PC and transfer data to the online database (Figure 5.8).

Figure 5.7: Software Preview function

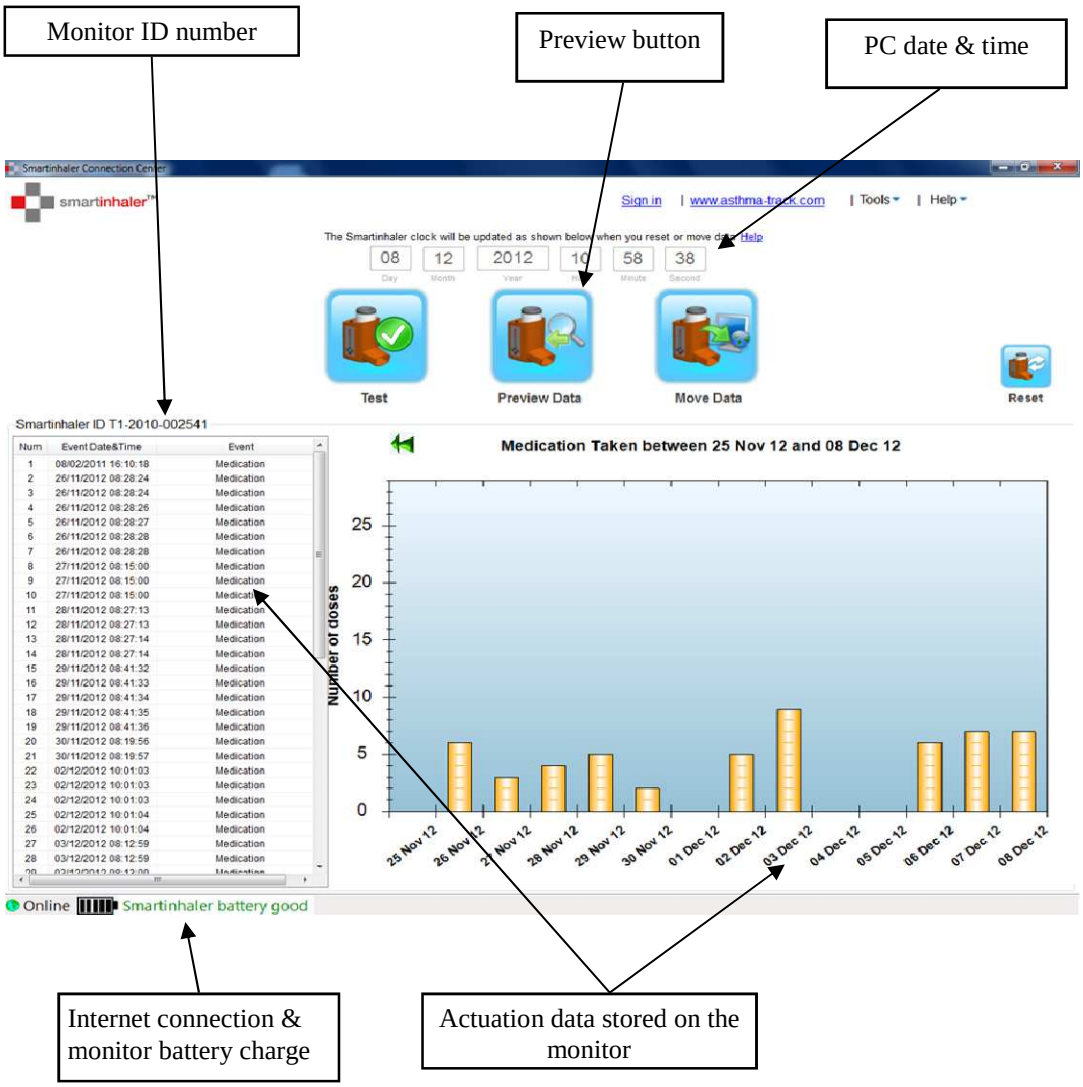
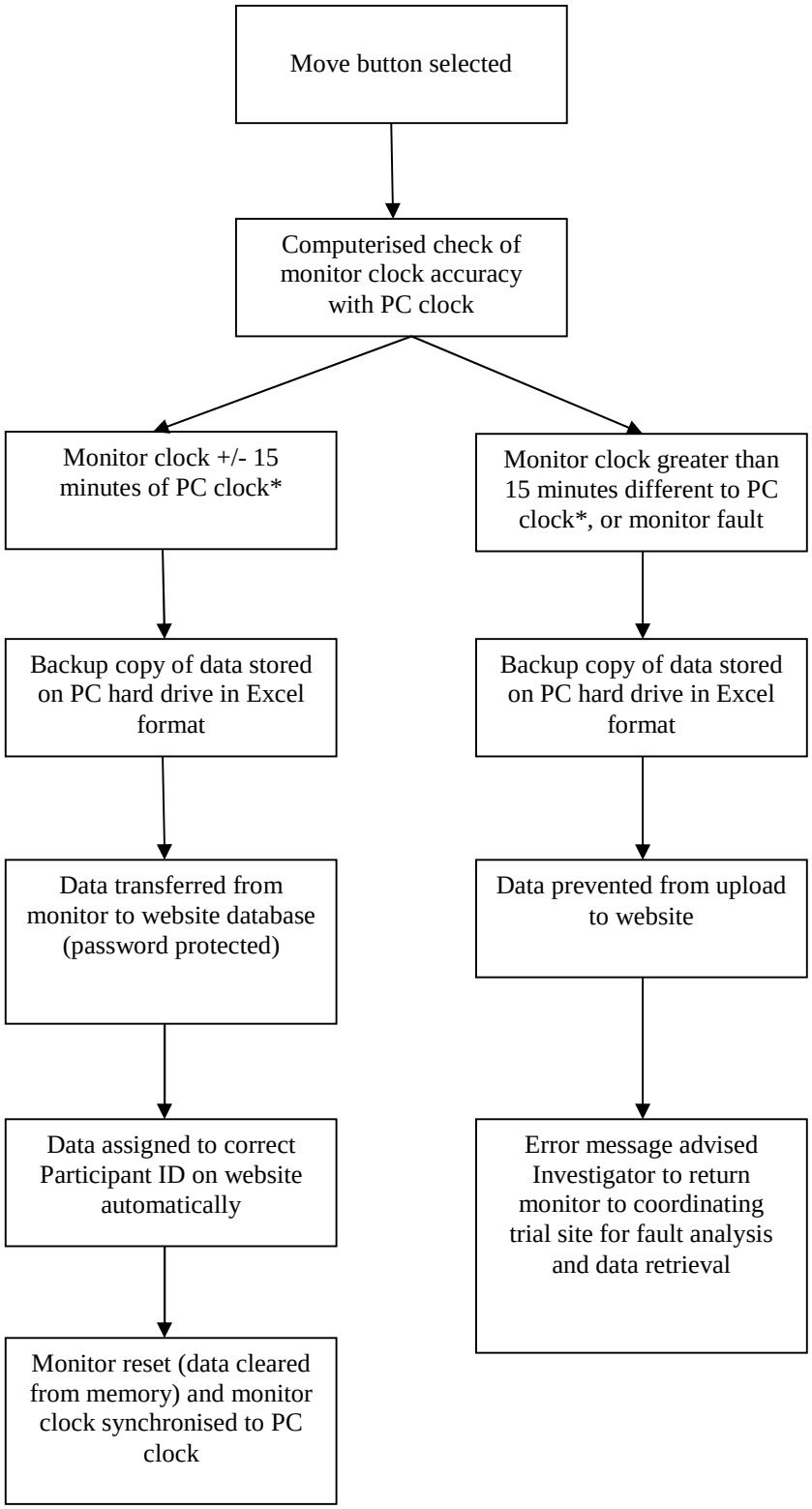


Figure 5.8: Computerised processes during data Move



* The product information for the Tracker monitor specified that the monitor clock accuracy was +/- 15 minutes per year without update. PC: Personal computer.

During successful data upload, investigators were prompted to enter a password to allow data transfer to the website database (Figure 5.9). The PC software was linked to the online database, so that data from the monitor was automatically allocated to the correct Participant ID on the website. After upload, the monitor was automatically reset (data was cleared from its memory) and investigators could reload the monitor with a new medication canister in preparation for dispensing at the next visit.

Excel files containing actuation data were automatically saved into a folder on the PC, identified by the date of upload and the Participant ID. One file was created for each monitor. Each file was labelled by the Participant ID, inhaler ID and date and time of upload. The monitor clock date and time were also saved in the file.

Data upload failure as a result of monitor clock fault or monitor damage resulted in an error message advising investigators to return monitors to the coordinating trial site for fault analysis, data retrieval and data cleanup (Figure 5.10). The process of fault identification and data retrieval occurred constantly throughout the study.

If connection to the internet was not available at the time of upload, then data was stored on the computer hard drive and automatically uploaded as above when an internet connection was sensed.

Data Move was performed for all returned monitors from participants, regardless of whether or not the participant had reported using the MDI. If no data was stored on the monitor, a backup (blank) Excel file was still created on the PC hard drive.

Figure 5.9: Software Move function: successful data upload

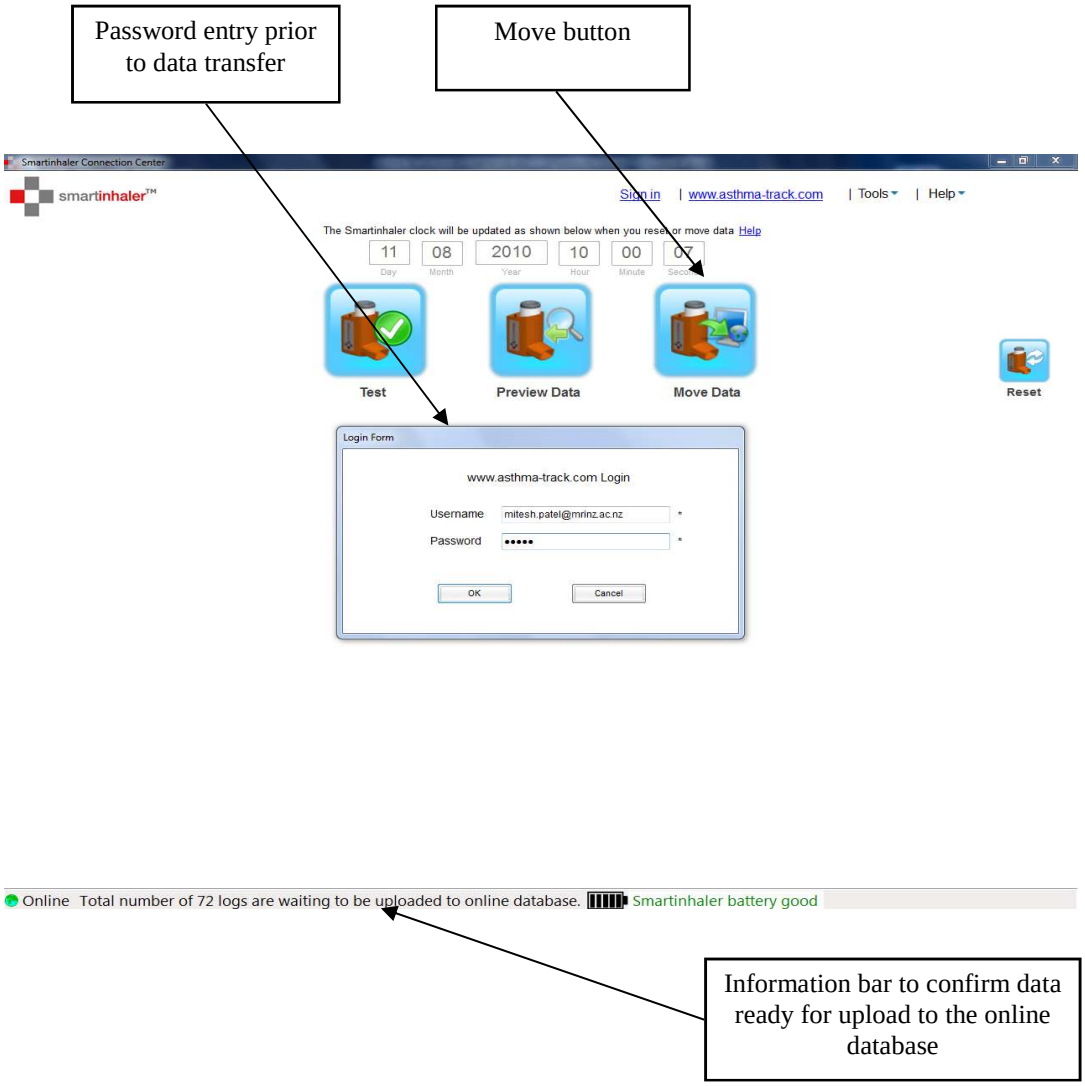
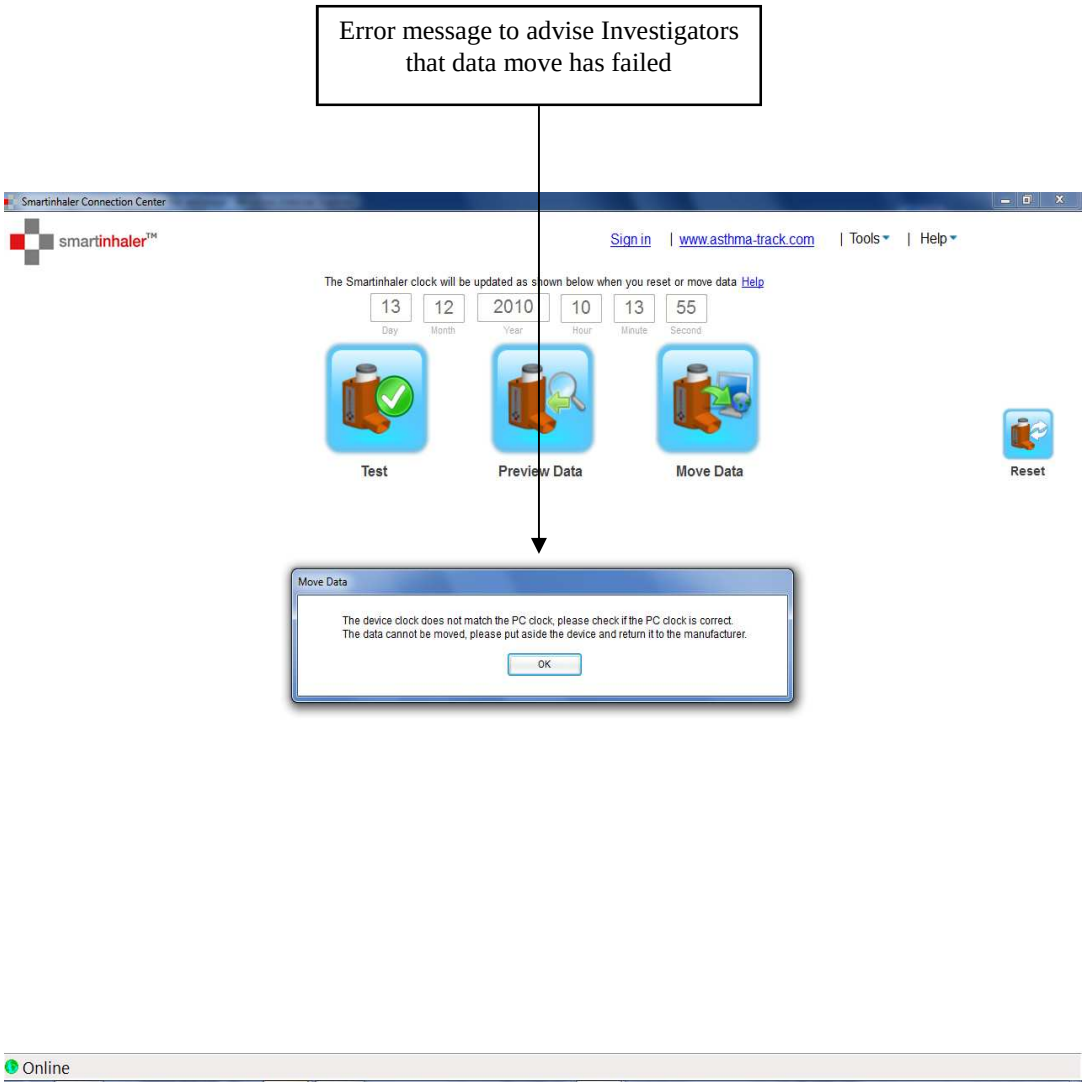


Figure 5.10: Monitor fault during data Move



5.6.3 Software 'Backup' function

The Backup function allowed investigators to copy data stored on the PC hard drive to a CD. This function allowed an off-site copy of the data to be made; thus, together with the primary website database, backup data was stored on the PC hard drive and a CD.

After data was uploaded from all MDIs returned by a participant, investigators were required to 'burn' a CD with the data from these monitors. Thus, one CD per visit per participant was created. After selecting the backup function on the software and inserting a blank CD into the PC, investigators were automatically prompted to a directory on the PC hard drive containing the backup data, in folders organised by date of upload and Participant ID (Figure 5.11 and Figure 5.12). After selecting the correct files for backup, data were backed up automatically to a CD.

Figure 5.11: Software Backup function (A)

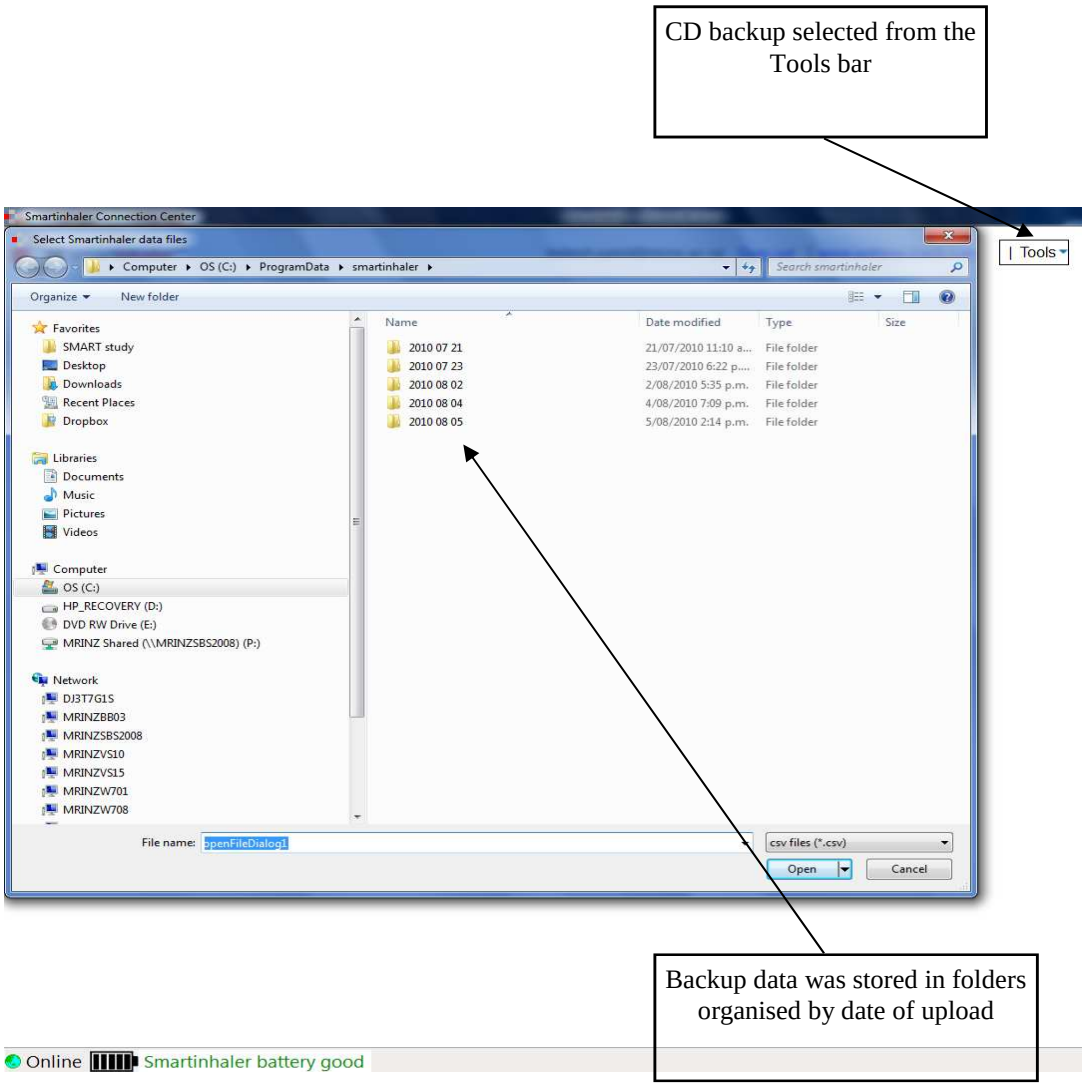
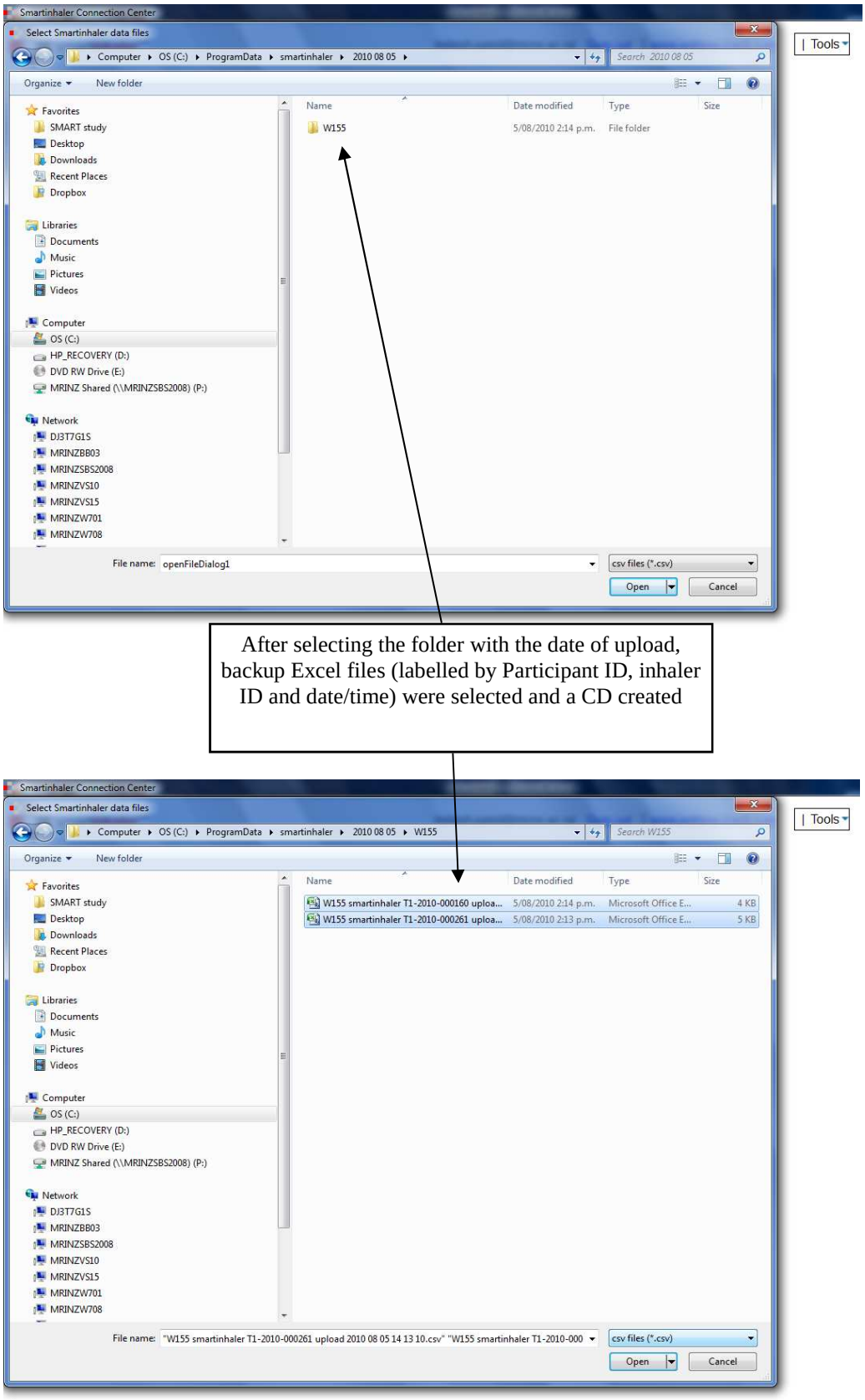


Figure 5.12: Software Backup function (B)



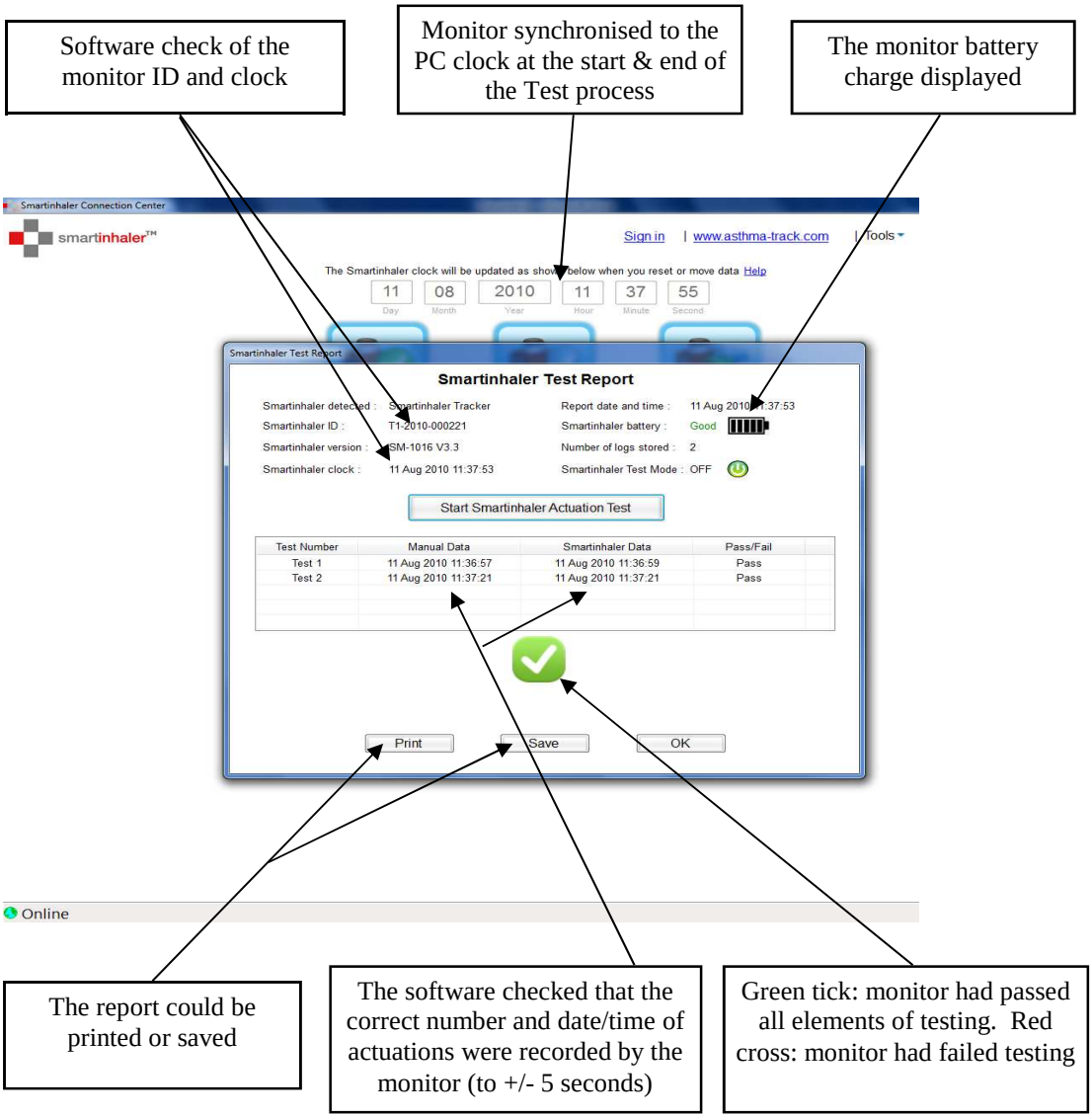
5.6.4 Software 'Test' function

The Test function was designed to allow computerised within-trial checks of monitor function.

After connecting the monitor to the PC, the Test function was selected. The monitor was automatically reset by the software. Investigators were prompted by the computer software to actuate the MDI twice; five seconds were allowed after prompting for actuation to occur. The software checked that the number and time/date of the two actuations performed were accurate (to within five seconds) and also checked the monitor battery charge.

At the end of the Test function, the monitor was automatically reset and the monitor clock synchronised with the computer. If all elements of monitor check were accurate, the software displayed a 'green tick' to inform the investigator that the MDI could be used in the trial. If any elements of the check failed, investigators were prompted with a 'red cross' and advised to remove the monitor from circulation and return it to the coordinating site (Figure 5.13). Test reports could be saved or printed for reference.

Figure 5.13: Software Test Function



5.6.5 Software 'Reset' function

This function cleared the monitor memory of all data and synchronised the monitor clock to the PC clock.

5.7 Within-trial monitor checking protocol

Monitors loaded with medication canisters were checked for correct functioning by investigators using the Test function described above, prior to dispensing to participants at Visits 2, 3, and 4. The purpose of these within-trial monitor checks was to ensure that there had been no loss of function in the period following pre-study checks and to identify damaged monitors prior to repeat dispensing. Investigators were advised to perform the checks in the 48-hours preceding the study visit.

5.8 Within-trial participant data check protocol

Data from the MDIs collected from participants at Visits 2, 3, 4 and 5 were uploaded using the Move function described above. The computer software automatically compared the monitor clock with the computer clock prior to data upload; a time discrepancy of more than 15 minutes prevented data upload and prompted the investigator to return the MDI to the coordinating site for analysis. The purpose of

this within-trial data check was to identify monitors with incorrect clocks prior to data transfer, thus reducing the risk of erroneous data being uploaded to the database. A 15 minute discrepancy was allowed as the product information for the Smartinhaler Tracker specifies that the monitor clock accuracy is +/- 15 minutes per year without update.

5.9 Website database of actuation data from uploaded MDIs

Data from uploaded MDIs was stored on a password-protected, website-based database (www.asthma-track.com). The coordinating trial site had complete access to the data on the website ('principal investigator access') and could supervise trial progress remotely. Investigators at trial sites had access restricted to that required to conduct the trial according to the protocol ('investigator access'). Investigator log-ins did not allow viewing of any uploaded inhaler data. Access to the website also provided training resources (Figure 5.14). The key features of the website are detailed below.

5.9.1 Participant study IDs

Study IDs were pre-allocated on the website, so that once randomisation had occurred, investigators could assign patient initials and date of birth to the relevant ID (Figure 5.15). Investigators were restricted in being able to view only participant IDs allocated to their own trial site.

Figure 5.14: Asthma-track website home page

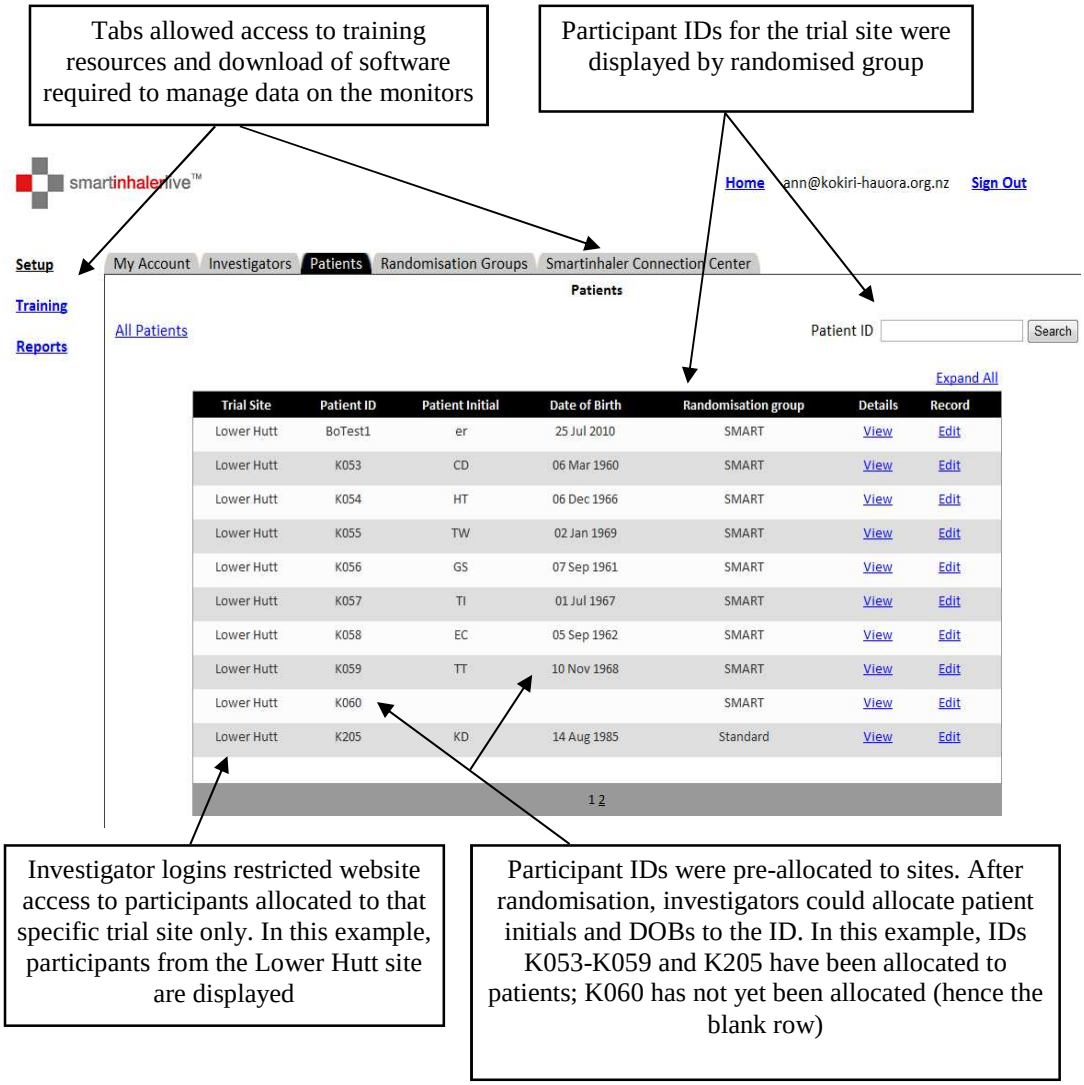
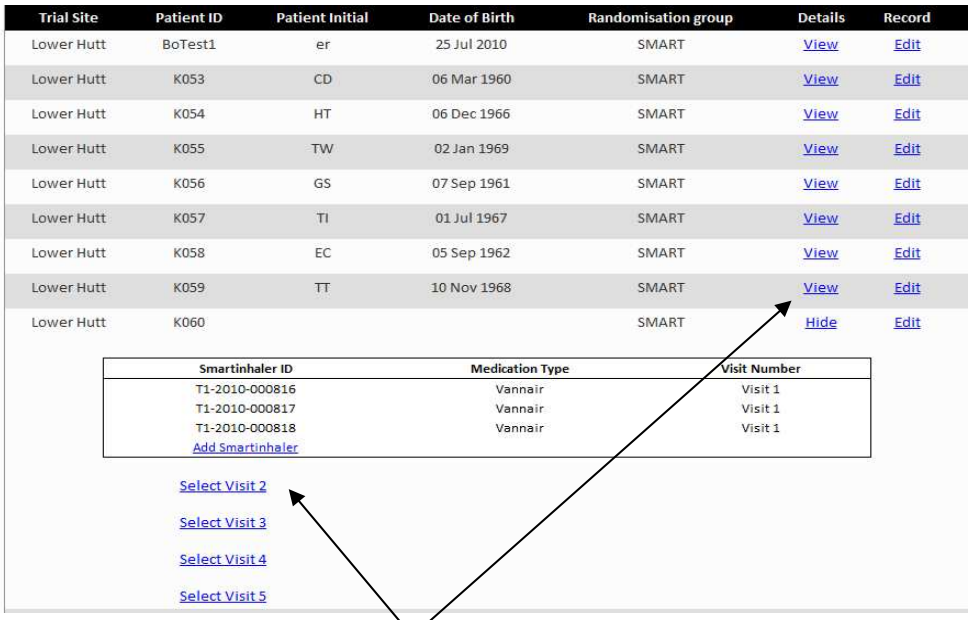


Figure 5.15: Viewing participants on the asthma-track website



Trial Site	Patient ID	Patient Initial	Date of Birth	Randomisation group	Details	Record
Lower Hutt	BoTest1	er	25 Jul 2010	SMART	View	Edit
Lower Hutt	K053	CD	06 Mar 1960	SMART	View	Edit
Lower Hutt	K054	HT	06 Dec 1966	SMART	View	Edit
Lower Hutt	K055	TW	02 Jan 1969	SMART	View	Edit
Lower Hutt	K056	GS	07 Sep 1961	SMART	View	Edit
Lower Hutt	K057	TI	01 Jul 1967	SMART	View	Edit
Lower Hutt	K058	EC	05 Sep 1962	SMART	View	Edit
Lower Hutt	K059	TT	10 Nov 1968	SMART	View	Edit
Lower Hutt	K060			SMART	Hide	Edit

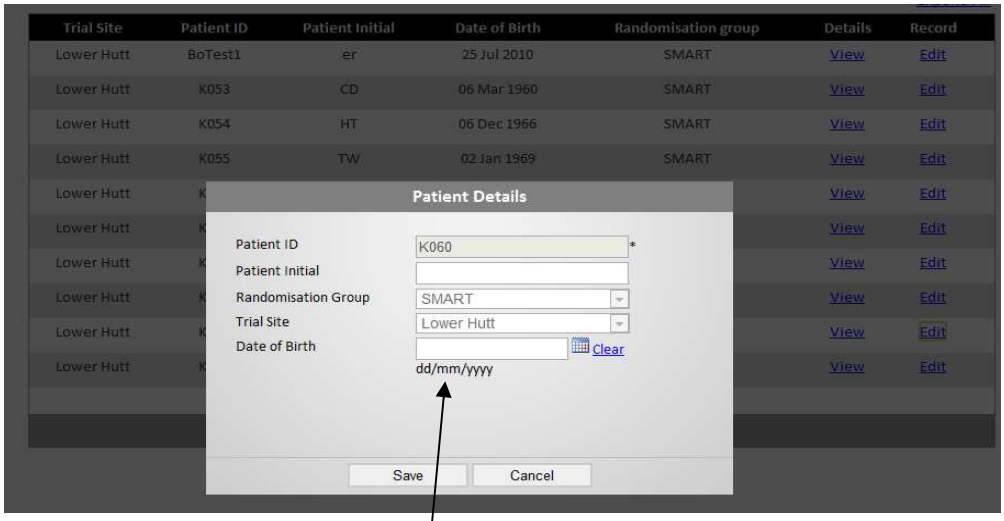
Smartinhaler ID	Medication Type	Visit Number
T1-2010-000816	Vannair	Visit 1
T1-2010-000817	Vannair	Visit 1
T1-2010-000818	Vannair	Visit 1
Add Smartinhaler		

Select Visit 2

Select Visit 3

Select Visit 4

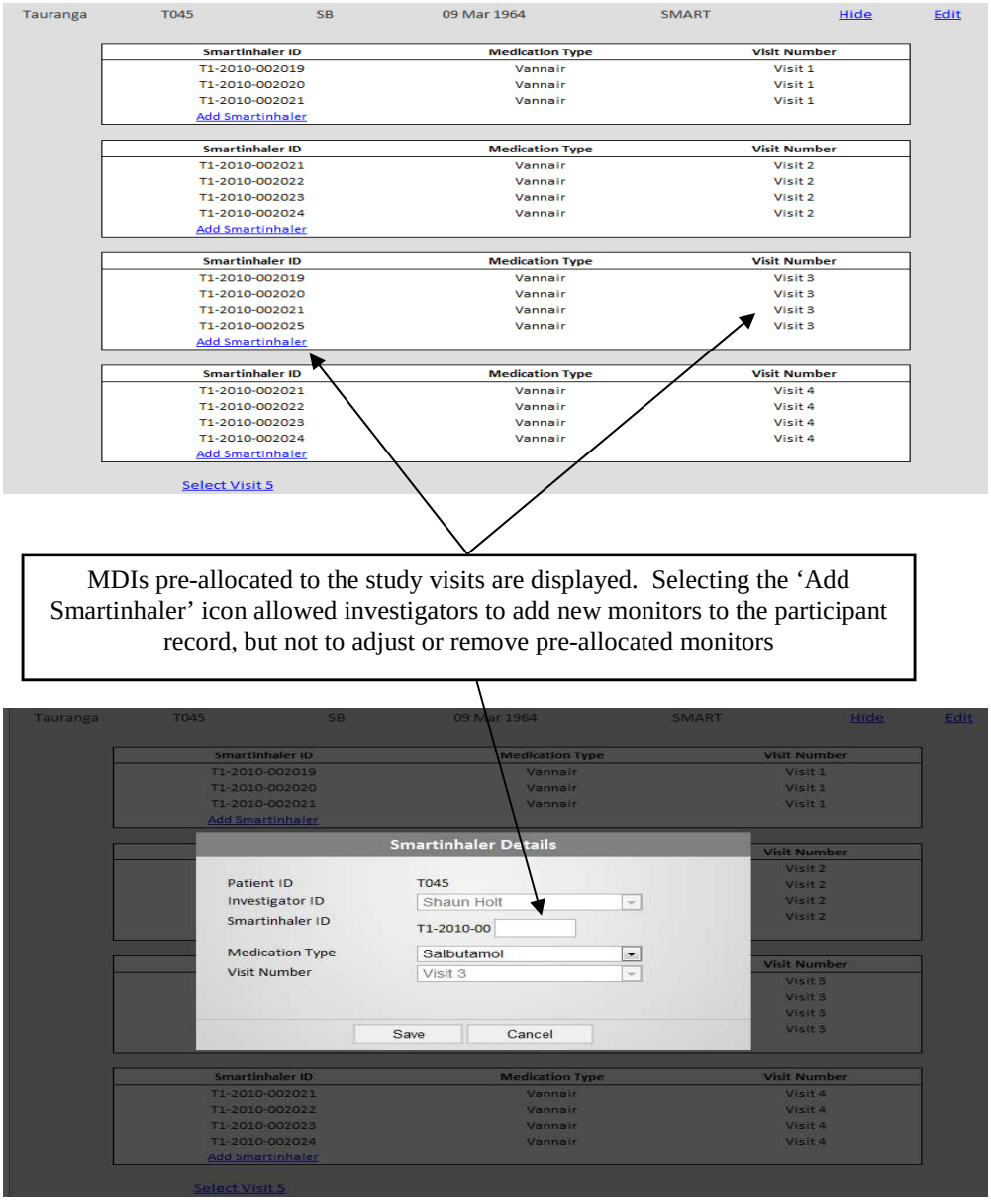
Select Visit 5



5.9.2 Monitor allocation

By selecting the 'View' icon, the MDIs pre-allocated to a Participant ID could be displayed by study visit (Figure 5.15). Investigators were able to add further MDIs to the participant record (for example, to replace a lost or damaged monitor), but were not able to alter or remove any pre-allocated MDIs (Figure 5.16).

Figure 5.16: Allocating MDIs to the website after randomisation



5.10 Website supervision by the coordinating trial site

Principal investigator access to the website allowed real-time supervision of trial sites. The website allowed the coordinating trial site to review data uploads from all sites (Figure 5.17), to track investigator login to the website (Figure 5.18) and to check if replacement monitors had been correctly assigned to a Participant ID.

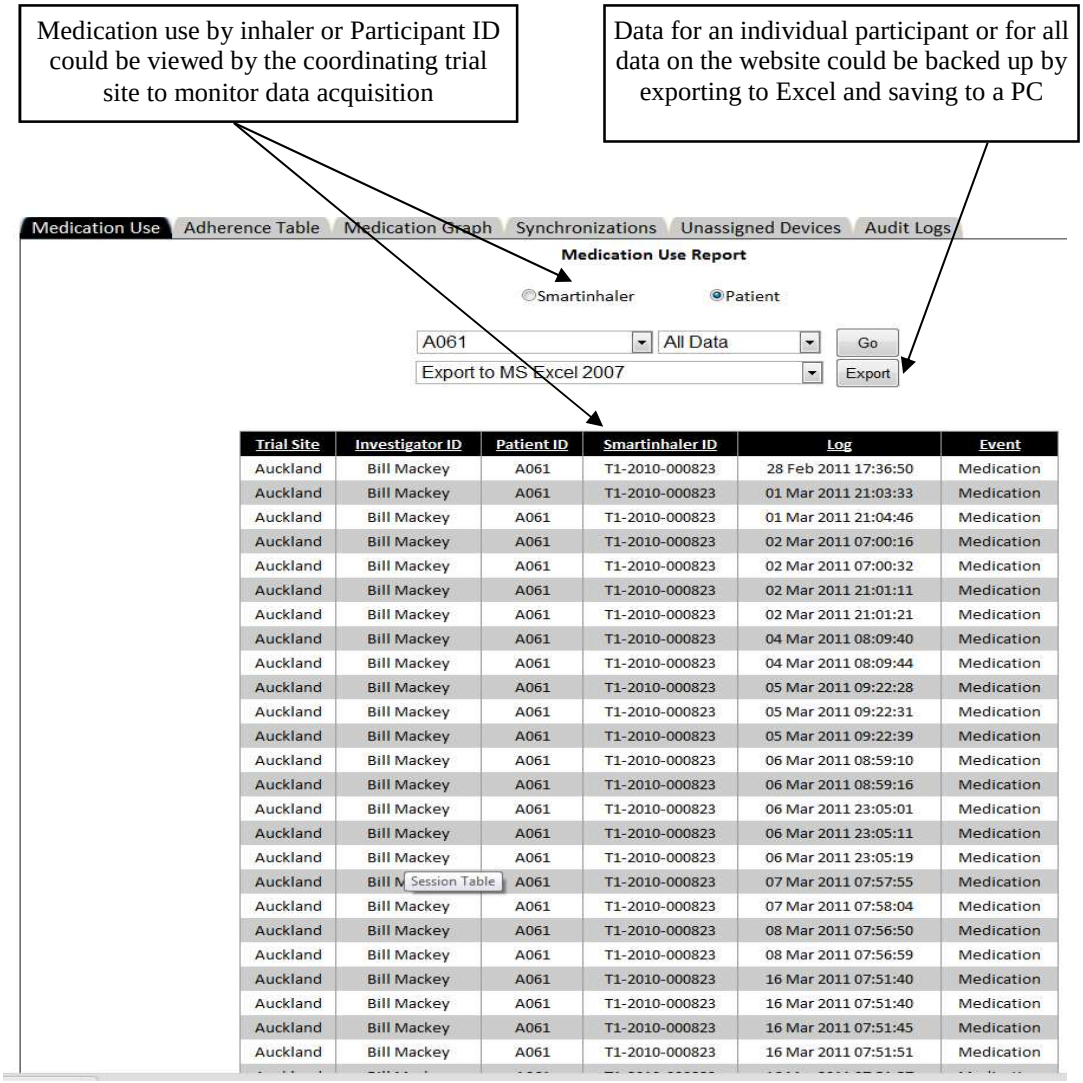
5.10.1 Electronic data supervision following Visit 1

By viewing assignment of patient initials and DOBs to the pre-allocated IDs on the website, the rate of recruitment at trial sites could be supervised. This was performed after the Visit 1 case record form documentation was received by the coordinating investigator.

5.10.2 Electronic data supervision summary for Visits 2 to 5

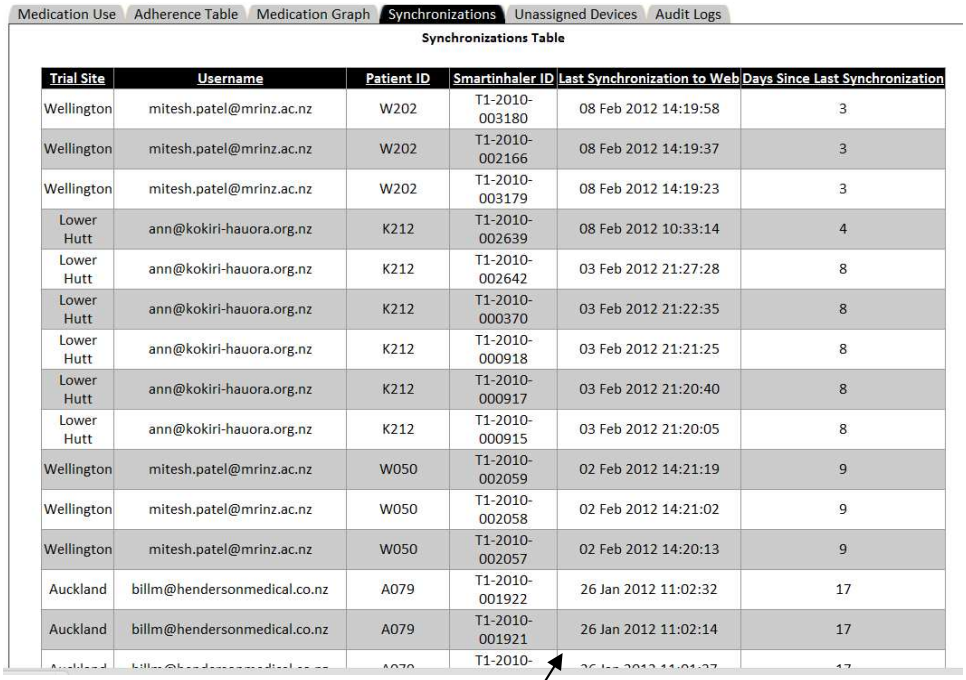
On completion of a study visit by an investigator, case record form documentation and CDs were forwarded to the coordinating trial site (Figure 5.19). CDs were checked to ensure the correct number of MDIs from the preceding study visit had been uploaded and backed-up. The website was then checked to ensure data from the upload had successfully transferred and that emergency inhalers (including any new monitors allocated to replace malfunctioning monitors) were correctly assigned.

Figure 5.17: Supervising data upload from trial sites



Trial Site	Investigator ID	Patient ID	Smartinhaler ID	Log	Event
Auckland	Bill Mackey	A061	T1-2010-000823	28 Feb 2011 17:36:50	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	01 Mar 2011 21:03:33	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	01 Mar 2011 21:04:46	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	02 Mar 2011 07:00:16	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	02 Mar 2011 07:00:32	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	02 Mar 2011 21:01:11	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	02 Mar 2011 21:01:21	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	04 Mar 2011 08:09:40	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	04 Mar 2011 08:09:44	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	05 Mar 2011 09:22:28	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	05 Mar 2011 09:22:31	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	05 Mar 2011 09:22:39	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	06 Mar 2011 08:59:10	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	06 Mar 2011 08:59:16	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	06 Mar 2011 23:05:01	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	06 Mar 2011 23:05:11	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	06 Mar 2011 23:05:19	Medication
Auckland	Bill M	A061	T1-2010-000823	07 Mar 2011 07:57:55	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	07 Mar 2011 07:58:04	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	08 Mar 2011 07:56:50	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	08 Mar 2011 07:56:59	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	16 Mar 2011 07:51:40	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	16 Mar 2011 07:51:40	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	16 Mar 2011 07:51:45	Medication
Auckland	Bill Mackey	A061	T1-2010-000823	16 Mar 2011 07:51:51	Medication

Figure 5.18: Supervising investigator logins and actions on the website



Medication Use | Adherence Table | Medication Graph | Synchronizations | Unassigned Devices | Audit Logs

Synchronizations Table

Trial Site	Username	Patient ID	Smartinhaler ID	Last Synchronization to Web	Days Since Last Synchronization
Wellington	mitesh.patel@mrinz.ac.nz	W202	T1-2010-003180	08 Feb 2012 14:19:58	3
Wellington	mitesh.patel@mrinz.ac.nz	W202	T1-2010-002166	08 Feb 2012 14:19:37	3
Wellington	mitesh.patel@mrinz.ac.nz	W202	T1-2010-003179	08 Feb 2012 14:19:23	3
Lower Hutt	ann@kokiri-hauora.org.nz	K212	T1-2010-002639	08 Feb 2012 10:33:14	4
Lower Hutt	ann@kokiri-hauora.org.nz	K212	T1-2010-002642	03 Feb 2012 21:27:28	8
Lower Hutt	ann@kokiri-hauora.org.nz	K212	T1-2010-000370	03 Feb 2012 21:22:35	8
Lower Hutt	ann@kokiri-hauora.org.nz	K212	T1-2010-000918	03 Feb 2012 21:21:25	8
Lower Hutt	ann@kokiri-hauora.org.nz	K212	T1-2010-000917	03 Feb 2012 21:20:40	8
Lower Hutt	ann@kokiri-hauora.org.nz	K212	T1-2010-000915	03 Feb 2012 21:20:05	8
Wellington	mitesh.patel@mrinz.ac.nz	W050	T1-2010-002059	02 Feb 2012 14:21:19	9
Wellington	mitesh.patel@mrinz.ac.nz	W050	T1-2010-002058	02 Feb 2012 14:21:02	9
Wellington	mitesh.patel@mrinz.ac.nz	W050	T1-2010-002057	02 Feb 2012 14:20:13	9
Auckland	billm@hendersonmedical.co.nz	A079	T1-2010-001922	26 Jan 2012 11:02:32	17
Auckland	billm@hendersonmedical.co.nz	A079	T1-2010-001921	26 Jan 2012 11:02:14	17
[illegible]	[illegible]	[illegible]	T1-2010-	[illegible]	[illegible]

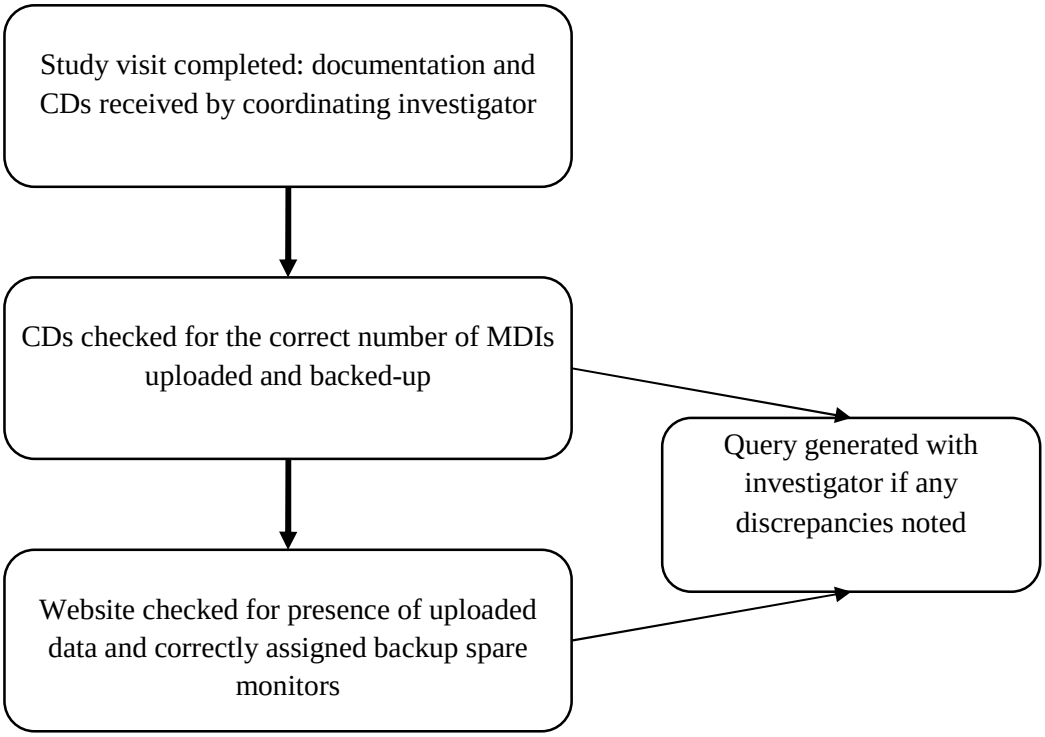
Investigator data uploads, login to the website and actions performed during login were all able to be supervised remotely by the coordinating trial site

Medication Use | Adherence Table | Medication Graph | Synchronizations | Unassigned Devices | Audit Logs

Audit Logs

Username	Activity	Page	Activity Date
mitesh.patel@mrinz.ac.nz	User logged in.	Login	11 Feb 2012 14:47:25
mitesh.patel@mrinz.ac.nz	User logged in.	Login	07 Feb 2012 12:26:03
mitesh.patel@mrinz.ac.nz	User logged in.	Login	03 Feb 2012 16:18:30
mitesh.patel@mrinz.ac.nz	User logged in.	Login	03 Feb 2012 15:20:46
mitesh.patel@mrinz.ac.nz	User logged in.	Login	31 Jan 2012 15:11:12
mitesh.patel@mrinz.ac.nz	User logged in.	Login	31 Jan 2012 10:04:24
mitesh.patel@mrinz.ac.nz	User logged in.	Login	31 Jan 2012 09:19:05
mitesh.patel@mrinz.ac.nz	User logged in.	Login	31 Jan 2012 08:36:57
mitesh.patel@mrinz.ac.nz	User logged in.	Login	30 Jan 2012 16:18:02
mitesh.patel@mrinz.ac.nz	User logged in.	Login	30 Jan 2012 15:50:20
mitesh.patel@mrinz.ac.nz	Add devices. PID =A296, Device ID =T1-2010-002725, Med Type = Salbutamol, Visit =Visit 4, InvID=	Patients	26 Jan 2012 11:08:49
mitesh.patel@mrinz.ac.nz	User logged in.	Login	26 Jan 2012 11:06:24
boq@smartinhaler.com	User logged in.	Login	26 Jan 2012 10:16:01
boq@smartinhaler.com	User logged in.	Login	26 Jan 2012 10:15:35
mitesh.patel@mrinz.ac.nz	User logged in.	Login	24 Jan 2012 15:26:54
mitesh.patel@mrinz.ac.nz	User logged in.	Login	24 Jan 2012 10:16:33
mitesh.patel@mrinz.ac.nz	User logged in.	Login	24 Jan 2012 10:02:49

Figure 5.19: Electronic data supervision summary for Visits 2 to 5



5.11 Summary of trial monitor and data checking protocols

The pre-study and within-study monitor checking protocols and the within-study data checking protocols are summarised in Table 5.1.

5.12 Summary

All electronic monitors were tested according to the pre-study use checks prior to packaging for use. Once packaged into boxes, allocation of monitors to Participant IDs was verified on both the spreadsheet log and online database, ensuring that every monitor was accounted for and traceable. All monitors underwent within-study monitor checking and data checking protocols. The computer software and online database were developed in order to safeguard data acquisition and allow remote supervision in the setting of a multicentre trial.

Table 5.1: Pre-study and within-study monitor and data checking protocol

Monitor checks	Pre-study monitor check *	Within-study monitor check †	Within-study data check †
Loading with medication canister ‡	X	X	
Reset §	X	X	X
Check for external structural faults	X	X	
Pre-study MDI actuations ‖	X		
Within-study MDI actuations ¶		X	
Diary log of actuations	X		
Computerised testing process		X	
Check of accuracy of number of actuations	X	X	
Check of accuracy of actuation time and date	X	X	
Check of monitor ID number **	X	X	
Check of battery charge	X	X	
Printable test report generated		X	
Preview of data stored on monitor ††	X		X
Computerised check of monitor clock accuracy ‡‡			X
Data from faulty monitors prevented from upload to website			X
Upload of data from functioning monitors to website			X
Data retrieval and cleanup from faulty monitors			X
Fault analysis for malfunctioning monitors	X	X	X

[Table legend is on the following page]

*: Pre-study checks were performed at the coordinating trial site prior to study use;
†: Within-study monitor checks and data checks were performed during trial use;
‡: The MDI was actuated during every canister reload to ensure firm insertion of the canister;
§: Data was cleared from the monitor memory and clock synchronised with the computer;
‖: The MDI was actuated twice, with a further two actuations at least 2 hours later;
¶: The MDI was actuated twice, prompted by computer software 'Test' function;
**: Each monitor had a unique identification (ID) number visible externally and on computer connection;
††: Visual inspection of data monitor without upload to the website;
‡‡: Computerised check of monitor clock accuracy to +/- 15 minutes of actual time.

5.13 Acknowledgements

The concept and design of the monitor Quality Control processes was primarily undertaken by Mitesh Patel and Richard Beasley, with input from Janine Pilcher, Justin Travers and Kyle Perrin. Pre-study monitor testing was performed by Mitesh Patel and Janine Pilcher and monitor packaging checks were performed by Maureen Stretch.

The details of these trial monitor protocols have been published: Patel, M., Pilcher, J., Travers, J., Perrin, K., Shaw, D., Black, P., Weatherall, M., & Beasley R. 2013. Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. *J Allergy Clin Immunol: In Practice,* 1, 83-91 [with permission to use from the publisher Elsevier].

Chapter Six: Results

6.1 Trial timelines

303 participants were enrolled between 29 June 2010 and 14 September 2011, with the last participant completing the study on 29 February 2012. The study timelines are summarised in Table 6.1. The recruitment of participants by site is shown in Table 6.2. Mitesh Patel recruited all the participants at the MRINZ site and also reviewed participants at the Tu Kotahi Māori Asthma Trust (Lower Hutt) site. All external site monitoring, trial coordination and Ethics reporting were performed by Mitesh Patel.

6.2 Dataset

Total follow-up time was 24,347 days (66.66 years) for the SMART group and 24,977 days (68.38 years) for the Standard group. Mean ± SD follow-up time was 161.2 ± 35.8 days per SMART participant and 164.3 ± 31.1 days per Standard participant. Mean ± SD treatment exposure was 155.8 ± 39.1 days per SMART participant and 159.2 ± 34.1 days per Standard participant.

One participant, who was ineligible due to a prior history of paroxysmal atrial fibrillation, was randomised to the SMART group and completed the study.

Table 6.1: Study timelines

Date	Milestone
October 2009	• Initial ethics application
	• Funding confirmed from the Health Research Council of New Zealand
February-April 2010	• Protocol updates
	• Electronic monitor testing
	• Monitor software development
	• Case record form drafting
	• Development of patient-seen documents (asthma plans, appointment cards, information sheets, consent forms)
	• Collaboration with Nexus6 and Lower Hutt site (Tu Kotahi Māori Asthma Trust)
	• Ethics re-submission
May 2010	• Full ethics approval
June 2010	• Clinical trial registration (ANZCTR 12610000515099)
	• Recruitment commencement (Wellington)
July 2010	• Set up of 2nd site (Lower Hutt)
September 2010	• Set up of 3rd site (Tauranga CentralMed GP)
December 2010	• 25% recruited
January 2011	• Set up of 4th site (Tauranga Papamoa Pines GP)
February 2011	• Set up of 5th site (Auckland Henderson Medical Centre GP)
March 2011	• 50% recruited
May 2011	• 75% recruited
August 2011	• 150 participants completed: interim safety statistical analysis performed
September 2011	• 100% recruited
February 2012	• Final participant completed
March-June 2012	• Hospital attendance validation performed
May 2012	• Database checks complete and analysis commenced

Table 6.2: Recruitment of participants by site

Site	Number of participants randomised
Tu Kotahi Māori Asthma Trust, Lower Hutt	15
CentralMed GP, Tauranga	96
Papamoa Pines GP, Tauranga	24
Henderson Medical Centre GP, Auckland	62
Medical Research Institute of New Zealand, Wellington	106
Total	**303**

Use of non-study inhalers (n=12 participants for SMART and n=9 participants for Standard) and sharing of inhalers (n=4 participants for SMART and n=3 participants for Standard) were reported infrequently.

Dose and duration for courses of systemic corticosteroids (including IV doses) were collected for all participants experiencing asthma exacerbations. All hospital attendances for asthma were verified with hospital records. Two extra ED visits for asthma were identified during the hospital database verification.

One extra SAE (a hospital admission for chest pain determined by the treating physicians to be non-cardiac in origin), was identified during the hospital database verification.

Out of a maximum possible 1515 study visits (five visits per patient, 303 randomised), 60 did not occur due to patient withdrawal, leaving 1455 potential visits. There were 11 non-attendances for visits; for seven of these visits, exacerbation, adverse effects and questionnaire data could be obtained by telephone. ACQ-7 results were measured for 1450 of 1455 visits (99.7%) (one non-completion of ACQ-7 and four non-attendances where telephone contact not possible). Interpolation for one missing value was performed for 12/1450 (0.83%) of the ACQ-7 questionnaires. FEV_1 results were measured for 1438 of 1455 visits (98.8%) (11 non-attendances, four participants declining spirometry and two non-completion of spirometry).

6.3 Protocol updates after study commencement

Protocol version 2 (dated 19 April 2010) was the current version at the time of trial commencement in June 2010. Updates to the protocol after trial commencement are detailed in Table 6.3.

6.4 Electronic monitor performance results

282,466 actuations from participant use of their inhalers over 49,149 days of treatment exposure were stored on the database at study completion.

Table 6.3: Protocol version updates after trial commencement

Date of update	Update details	Rationale
9 September 2010 (to protocol version 3)	Inclusion Criteria: Clarification of exacerbation definition for patients who self-administer prednisone	A proportion of severe asthmatics will have been prescribed prednisone by their physician or GP for self-administration at home in the event of an exacerbation, as per their self-management plan. Prednisone use for at least 3 days fulfils the definition of a severe asthma exacerbation used in the ATS/ERS consensus asthma clinical trial guidelines (Reddel et al., 2009) and so the wording of this inclusion criterion was updated in order to allow eligibility to the study for these patients.
	Exclusion Criteria: Clarification of use of a home nebuliser	Patients with asthma who used a home nebuliser were eligible to enter the study if they agreed to withhold nebuliser use for the study duration, as discussed with the patient by the investigator at the first visit.
	Visit 1	Three, rather than two, Vannair inhalers were provided to each patient in the SMART group at Visit 1, to allow patients greater flexibility when using their inhalers.
20 October 2010 (to protocol Version 4)	Prior Intensive Care Unit (ICU) admission removed as an exclusion criterion	As the study aimed to study the potential benefits of the SMART regimen specifically in severe and high-risk asthmatics, patients who had prior ICU admissions for asthma formed part of the target group for this study. The removal of prior ICU admission as an exclusion criterion therefore allowed a representative group of severe asthmatics to be eligible for this study.

Protocol version 2 (dated 19 April 2010) was the current version at the time of trial commencement in June 2010.

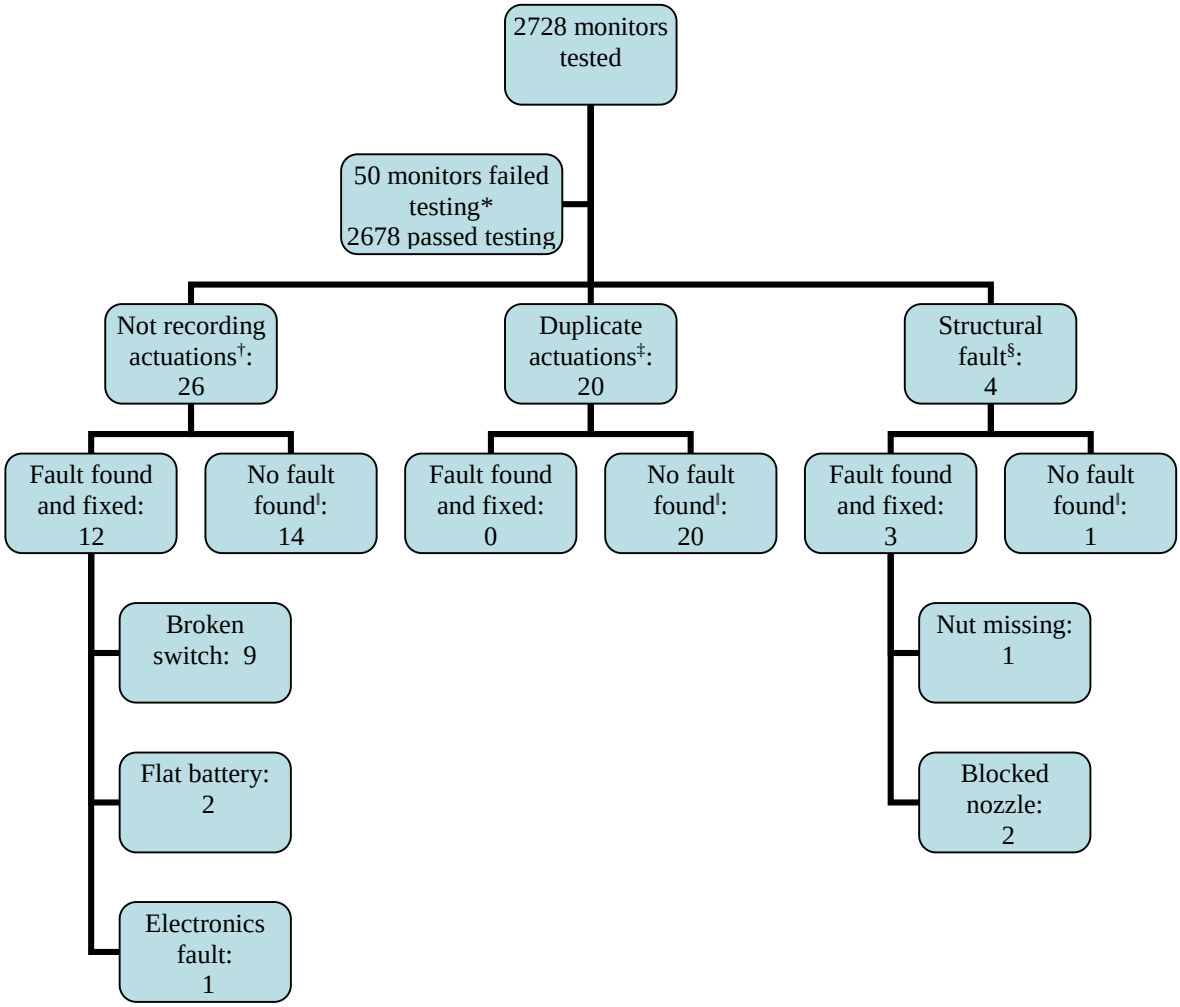
6.4.1 Pre-study monitor checks

2728 monitors in total (839 salbutamol monitors and 1889 budesonide/formoterol monitors) underwent pre-study checks. 2678 of the 2728 monitors tested (98.2%) passed this check (Figure 6.1). Of the 50 monitors which failed testing, 26 did not record actuations that were performed, 20 recorded extra actuations and four had structural faults. Of these 50 monitors, 15 were subsequently repaired and passed for use in the trial, while the remaining 35 monitors were not utilised any further.

6.4.2 Within-study monitor checks

2642 monitors (806 salbutamol monitors and 1836 budesonide/formoterol monitors) were dispensed to patients in the trial. A total of 93 of 2642 monitors (3.5%) (33 budesonide/formoterol monitors in the SMART group and 29 budesonide/formoterol and 31 salbutamol monitors in the Standard group) were lost or thrown away by participants during the study.

Figure 6.1: Monitors identified as faulty during pre-study use checks



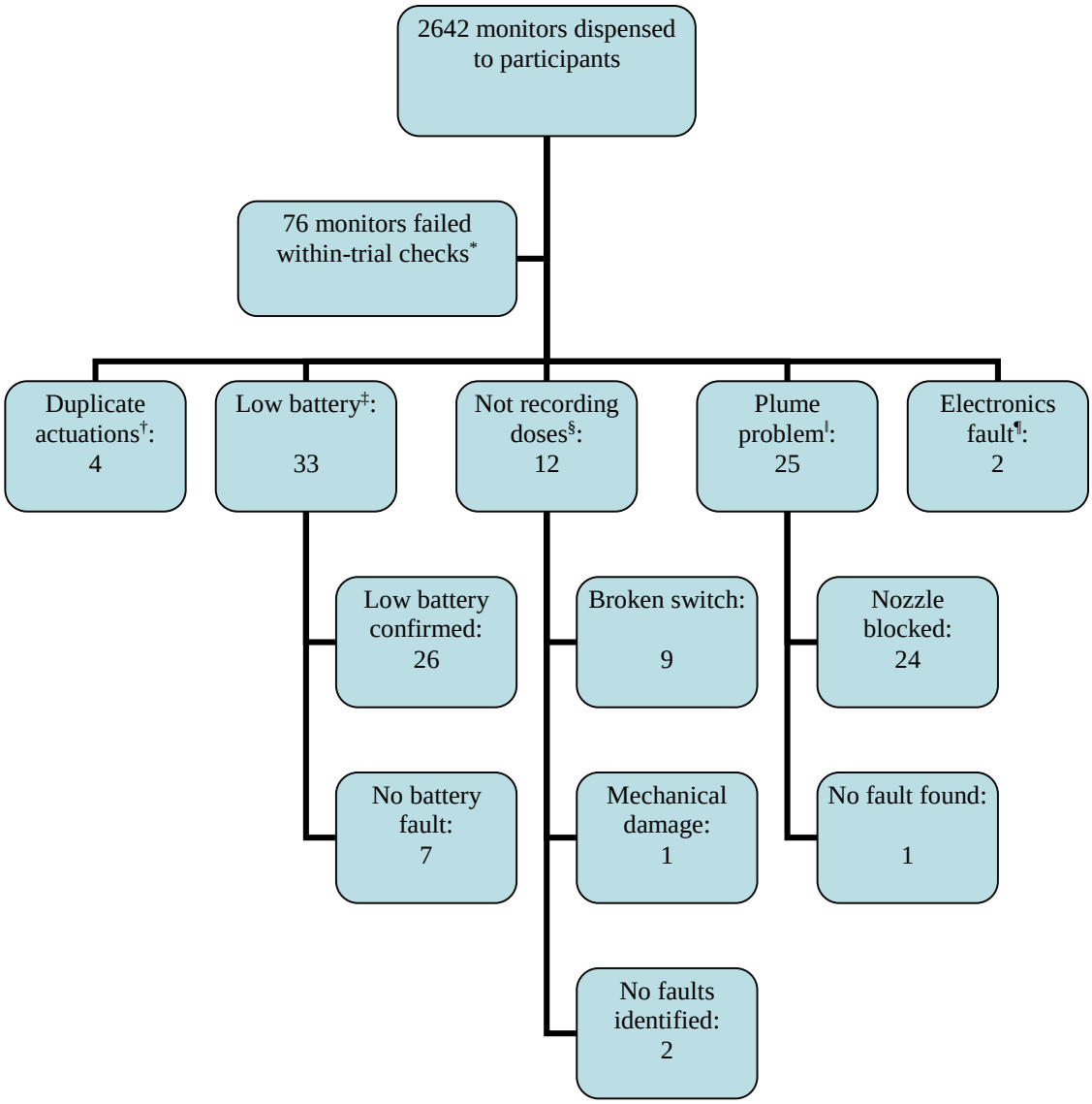
*: 27 budesonide/formoterol monitors and 23 salbutamol monitors; †: 10 budesonide/formoterol monitors and 16 salbutamol monitors; ‡: 16 budesonide/formoterol monitors and 4 salbutamol monitors; §: 1 budesonide/formoterol monitors and 3 salbutamol monitors; ‖: these devices were not reused in the trial.

There were 76 monitors (2.9% of the total dispensed) that failed testing and were removed from trial use by investigators as a result of the within-study monitor checking process (Figure 6.2). 33 of these monitors failed testing because the battery was not fully charged; in 31/33 of these monitors, actuation recording was not affected. 25 monitors failed checks due to a medication plume fault as a result of MDI nozzle blockage and 12 did not record test actuations correctly. Four monitors were found to record duplicate actuations.

6.4.3 Within-study participant data checks

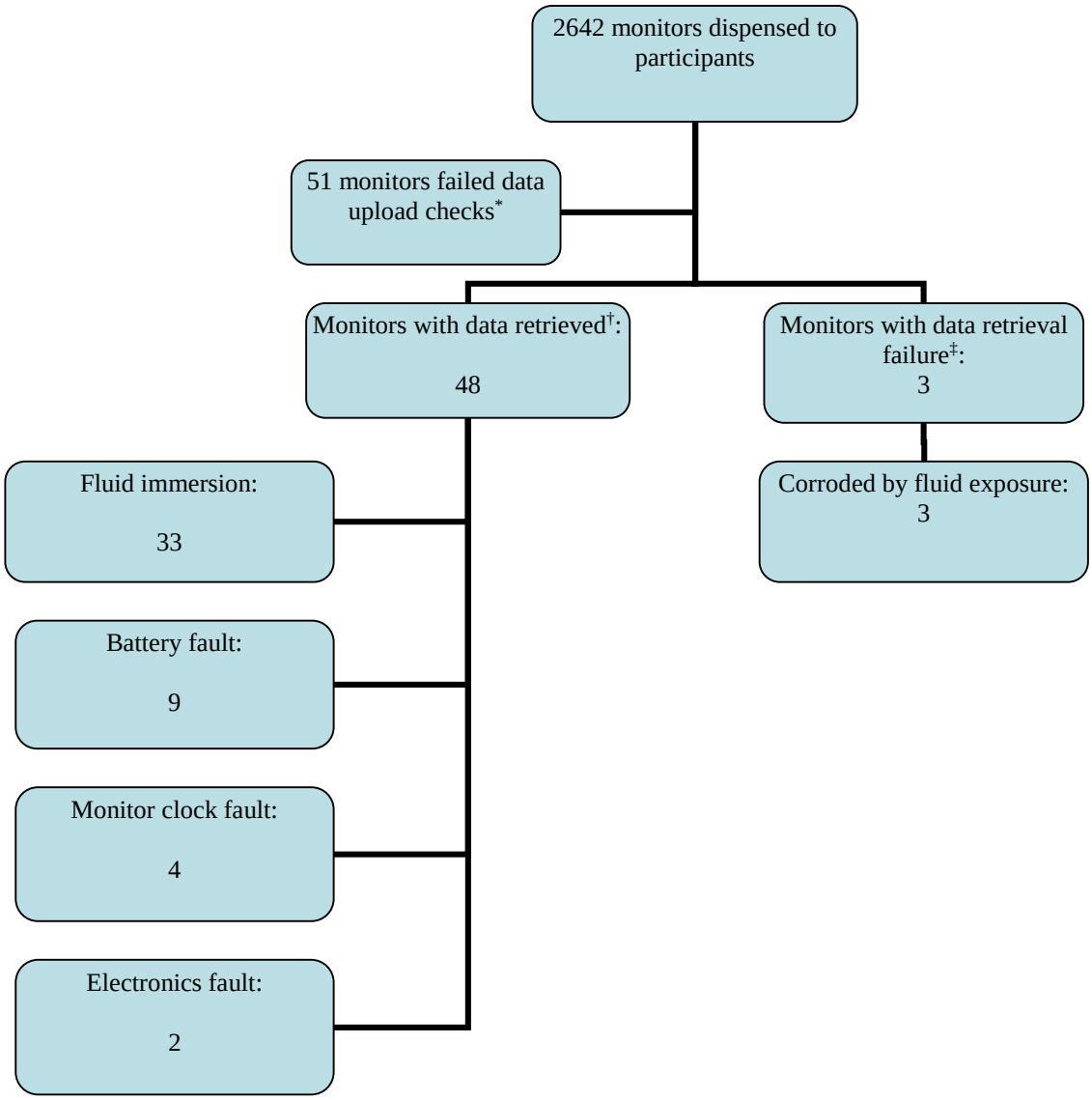
There were 51 monitors (1.9% of the total dispensed) which failed the data upload checks (Figure 6.3). In all cases, data was stored on the monitor from use of the MDI during the preceding study window. An error message from the computer software alerted the investigator that there was a fault preventing data transfer or that the monitor clock had malfunctioned. In the majority of monitors, evidence of fluid immersion as the cause for malfunction was determined during manufacturer analysis. All of these monitors were returned to the manufacturer and in 48, data could be retrieved to the point of monitor malfunction. In three monitors, data extraction was unable to be performed due to the severity of fluid damage.

Figure 6.2: Monitors identified as faulty during within-study checks at Visits 2 to 4



*: 37 budesonide/formoterol monitors and 39 salbutamol monitors; †: 3 budesonide/formoterol monitors and 1 salbutamol monitor (no fault found on these monitors; not reused in the trial); ‡: 23 budesonide/formoterol monitors and 10 salbutamol monitors; §: 7 budesonide/formoterol monitors and 5 salbutamol monitors; ‖: 4 budesonide/formoterol monitors and 21 salbutamol monitors; ¶: 2 salbutamol monitors.

Figure 6.3: Monitors identified as faulty during within-study data upload checks at Visits 2 to 5



*: 32 budesonide/formoterol monitors and 19 salbutamol monitors; †: 29 budesonide/formoterol monitors and 19 salbutamol monitors; ‡: 3 budesonide/formoterol monitors.

6.4.4 Overall monitor performance

93/2642 (3.5%) monitors were lost or thrown away by participants. 51/2642 (1.9%) monitors malfunctioned prior to data upload. Complete data was therefore available from 2498/2642 (94.5%) of dispensed monitors and 2498/2549 (98.0%) of returned monitors.

6.5 Electronic medication use data on study visit days

After removal of medication use data from study visit days (n=11,576 actuations), 270,890 actuations were included in the analyses.

6.6 Interim statistical safety analysis

2/85 (2.35%) participants randomised to the SMART group had at least one hospital admission for asthma; one participant had one and the other had two admissions. 2/82 (2.44%) participants randomised to the Standard group had one hospital admission each for asthma, a total of two hospital admissions.

The total number of participants with at least one hospital admission for asthma was 4/167, 2.40% (95% CI 0.66 to 6.0). The p value for whether the proportion was different to 4.5% was 0.25. There was therefore no evidence that the proportion of

participants with at least one hospital admission for asthma was different from the pre-specified reference rate.

2/85 (2.35%) participants randomised to the SMART group and 2/82 (2.44%) participants randomised to the Standard group had at least one hospital admission for asthma. The Relative risk of admission SMART versus Standard was 0.96 (95% CI 0.14 to 6.7), Fishers exact p=1.0.

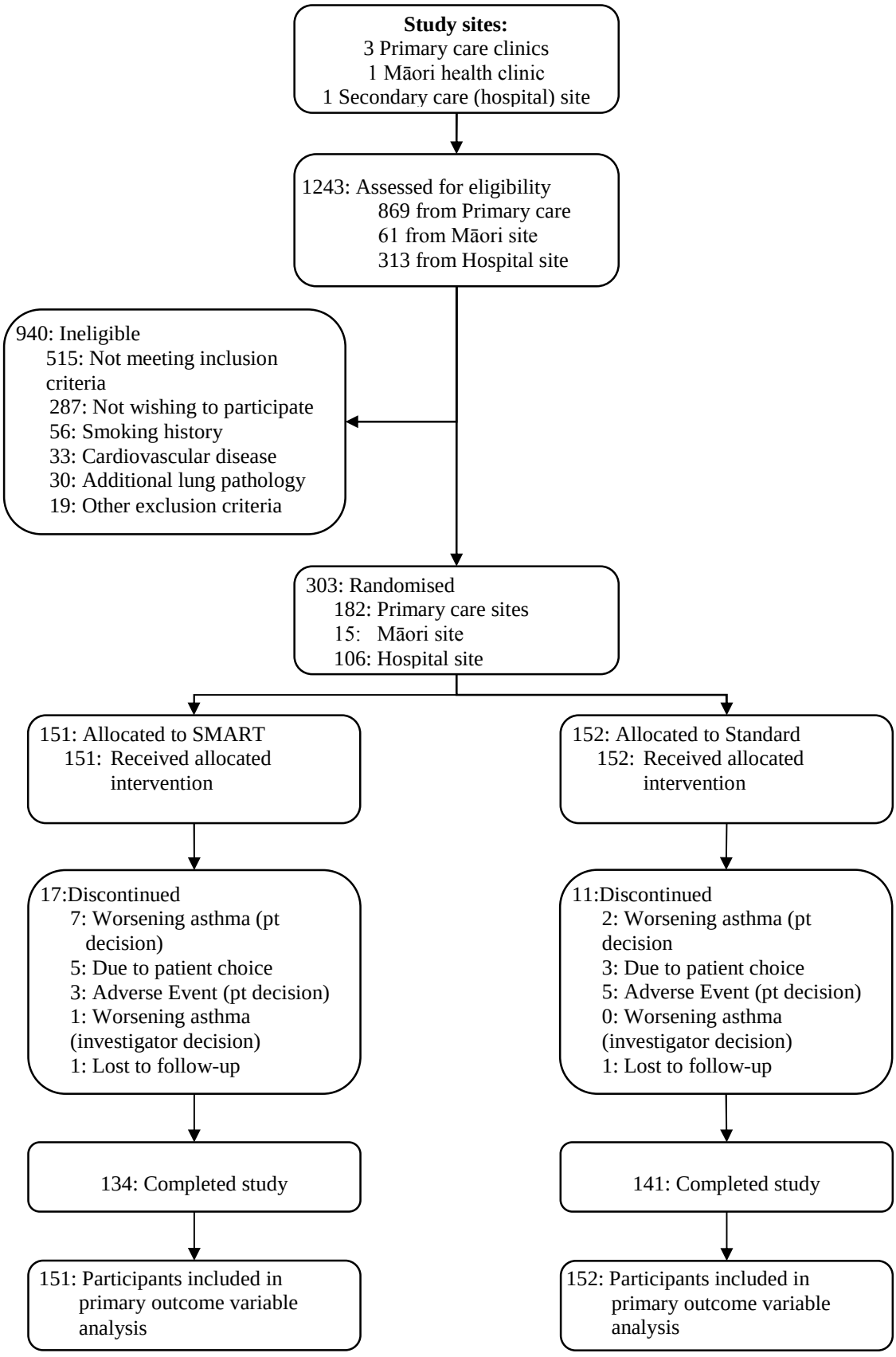
There were three hospital admissions for asthma in 85 participants in the SMART group and two hospital admissions for asthma in 82 participants in the Standard group. The Relative rate of hospital admissions for asthma SMART versus Standard was 1.4 (95% CI 0.24 to 8.3), p=0.69.

There was therefore no evidence that the rate of hospital admissions for asthma overall was different from 4.5% or that there was any difference in the rate of hospital admissions for asthma by treatment group. The independent safety monitor, Dr Andrew Brant, did not recommend a safety review for the study.

6.7 Study flow of participants

Study flow of participants is shown in Figure 6.4.

Figure 6.4: Study flow of participants



Pt: Patient

940/1243 (75.6%) of patients screened were ineligible for study entry. 515/940 (54.8%) of these patients did not meet eligibility criteria as they had not experienced an asthma exacerbation in the preceding 12 months or were not on ICS, and therefore were outside the target group of 'at-risk' patients.

Loss to follow-up occurred infrequently (2/303 (0.7%) of participants). A final visit assessment was completed in 21/28 (75%) participants who otherwise withdrew from the study. All patients randomised to treatment were included in the analysis for the primary outcome.

6.8 Baseline characteristics of participants

Baseline characteristics of participants are shown in Table 6.4.

Approximately 60% of participants had poorly controlled asthma at baseline, as measured by ACQ-7 score. 90% of participants had at least one severe asthma exacerbation in the 12 months preceding study entry. 40% of participants had 2 or more severe asthma exacerbations in the preceding 12 months.

Baseline budesonide dose was approximately 800µg and approximately 65% of participants were on LABA therapy pre-study. Half of the 303 participants had a step-up of therapy at study entry, as defined by GINA criteria (GINA, 2011).

Table 6.4: Baseline characteristics of trial participants*

Characteristic	SMART group (N = 151)	Standard group (N = 152)
Age, years		
Mean±SD	41.3±13.7	42.6±14.5
Median (IQR)	41.6 (29.2 to 52.3)	42.4 (31.0 to 56.0)
Male gender, n (%)	48 (31.8)	46 (30.3)
Ethnicity, n (%)		
European	113 (74.8)	118 (77.6)
Māori	25 (16.6)	19 (12.5)
Pacific Islander	5 (3.3)	10 (6.6)
Other	8 (5.3)	5 (3.3)
Duration of asthma, years		
Mean±SD	26.7±14.5	26.2±14.6
Median (IQR)	25 (17 to 36)	23 (15 to 36)
ACQ-7 Score		
Mean±SD	1.87±0.96	1.90±1.13
Median (IQR)	1.86 (1.14 to 2.57)	1.71 (1.14 to 2.43)
Number of participants with:		
Score ≤ 0.75, n (%)	20 (13.2)	24 (15.8)
Score 0.76 – 1.49, n (%)	34 (22.5)	39 (25.7)
Score ≥1.5, n (%)	97 (64.2)	89 (58.6)
On-treatment FEV_1, Litres		
Mean±SD	2.62±0.91	2.50±0.78
Median (IQR)	2.54 (2.00 to 3.07)	2.48 (1.92 to 3.01)
On-treatment FEV_1 % predicted		
Mean±SD	81.6±18.9	80.4±20.5
Median (IQR)	82.1 (69.8 to 93.8)	82.5 (66.1 to 91.9)
Number of participants with:		
FEV_1 <40 % predicted, n (%)	0 (0)	3 (2.0)

FEV_1 40 - <60 % predicted, n (%)	22 (14.6)	25 (16.4)
FEV_1 60 - <80 % predicted, n (%)	46 (30.5)	39 (25.7)
FEV_1 80 - <100 % predicted, n (%)	58 (38.4)	61 (40.1)
FEV_1 ≥100 % predicted, n (%)	25 (16.6)	24 (15.8)
Severe exacerbations in the prior 12 months		
Mean±SD	1.55±1.31	1.73±1.22
Median (IQR)	1 (1 to 2)	1 (1 to 2)
Number of participants with:		
0 severe exacerbations, n (%)	14 (9.3)	11 (7.2)
1 severe exacerbation, n (%)	86 (57.0)	75 (49.3)
2 severe exacerbations, n (%)	29 (19.2)	31 (20.4)
3 severe exacerbations, n (%)	10 (6.6)	22 (14.5)
4 severe exacerbations, n (%)	5 (3.3)	6 (3.9)
≥ 5 severe exacerbations, n (%)	7 (4.6)	7 (4.6)
Number of hospital admissions ever for asthma		
Mean±SD	3.13±6.13	4.64±10.90
Median (IQR)	1 (0 to 4)	1 (0 to 4)
Medication use		
Daily ICS dose (budesonide or equivalent), µg		
Mean±SD	804.5±352.7	812.6±370.4
Median (IQR)	800 (800 to 800)	800 (800 to 800)
LABA, n (%)	92 (60.9)	103 (67.8)
Combination ICS/LABA inhaler, n (%)	73 (48.3)	82 (53.9)
Step-up, n (%)	76 (50.3)	64 (42.1)
Step-neutral, n (%)	75 (49.7)	88 (57.9)
ICS dose reduction, n (%)	14 (9.3)	15 (9.9)
Self-reported reliever use as per ACQ question 6, median (IQR)	2 (1 to 3)	2 (1 to 3)
Number of participants with:		
Self-report score of 0, n (%)	26 (17.2)	22 (14.5)
Self-report score of 1, n (%)	45 (29.8)	49 (32.2)
Self-report score of 2, n (%)	39 (25.8)	40 (26.3)

Self-report score of 3, n (%)	25 (16.6)	21 (13.8)
Self-report score of 4, n (%)	8 (5.3)	11 (7.2)
Self-report score of 5, n (%)	5 (3.3)	3 (2.0)
Self-report score of 6, n (%)	3 (2.0)	6 (3.9)
Spacer use, n (%)	75 (49.7)	75 (49.3)
Pre-study use of a written asthma self-management plan, n (%)	15 (9.9)	20 (13.2)
Use of within-study symptoms-based plan, n (%)	125 (82.8)	125 (82.2)
Use of within-study peak flow-based plan, n (%)	26 (17.2)	27 (17.8)
Current smokers, n (%)	30 (19.9)	29 (19.1)
Pack year history:		
Mean±SD	9.5±8.8	12.5±11.6
Median (IQR)	7 (3 to 12)	9 (4 to 16)
Ex-smokers, n (%)	49 (32.5)	48 (31.6)
Pack year history:		
Mean±SD	8.3±8.5	8.1±10.4
Median (IQR)	5 (1 to 10)	4 (2 to 10)
Non-smokers, n (%)	72 (47.7)	75 (49.3)
Pregnant during study participation, n (%)	4 (2.6)	5 (3.3)

* Plus-minus values are means ± SD. IQR: Inter-quartile range. A severe exacerbation is defined as the use of systemic corticosteroids for at least 3 days; or, a hospitalisation or ED visit because of asthma, requiring systemic corticosteroids. Courses of corticosteroids separated by 7 days or more were treated as separate severe exacerbations. ACQ-7 score is a composite score of asthma control, comprising questions on asthma symptoms, rescue bronchodilator use and FEV_1 % predicted (overall scores range from 0 to 6, with scores ≤0.75 suggesting 'well-controlled' asthma and scores ≥1.50 suggesting 'not well-controlled' asthma).

ICS dose conversion: 500µg fluticasone = 800µg budesonide; 1000µg beclomethasone = 800µg budesonide. Low daily budesonide dose was defined as 200-400µg; medium daily budesonide dose was defined as >400-800µg; high daily budesonide dose was defined as >800µg. Step-up patients were defined as having no pre-study treatment with LABA (at any ICS dose) or pre-study treatment with low dose budesonide and LABA; step-neutral was defined as pre-study treatment with medium or high dose budesonide and LABA. ICS dose reduction was defined as the subgroup of step-neutral patients who were on pre-study high dose budesonide and LABA [based on GINA (2011)].

ACQ question 6 is a categorical score of reliever use over the preceding 7 days in the following bands: score 0, none; score 1, 1 to 2 salbutamol inhalations most days; score 2, 3 to 4 salbutamol inhalations most days; score 3, 5 to 8 salbutamol inhalations most days; score 4, 9 to 12 salbutamol inhalations most days; score 5, 13 to 16 salbutamol inhalations most days; score 6, more than 16 salbutamol inhalations most days.

There are no missing data from Table 6.4.

80% of participants were provided with a symptoms-based asthma self-management plan and 20% a peak-flow based plan for use during the study.

6.9 Primary outcome variable

There was no significant difference in the proportion of participants with at least one high use episode: SMART 84/151 (55.6%) versus Standard 68/152 (44.7%), relative risk (95% CI) 1.24 (0.99 to 1.56), p=0.058 (Table 6.5). In the sensitivity analysis, which also incorporated the overuse of budesonide/formoterol in the Standard group, there was no significant difference in the proportion of participants with at least one high use episode: SMART 84/151 (55.6%) versus Standard 94/152 (61.8%), relative risk (95% CI) 0.90 (0.74 to 1.09), p=0.27 (Table 6.5).

Table 6.5: Primary outcome variable

Outcome	SMART group (N = 151)	Standard group (N = 152)	Relative Risk SMART vs Standard (95% CI)	P value
Primary outcome				
At least one episode of high use, n (%)	84 (55.6)	68 (44.7)	1.24 (0.99 to 1.56)	0.058
At least one episode of high use (adjusted for budesonide/formoterol use above maintenance in Standard), n (%)*	84 (55.6)	94 (61.8)	0.90 (0.74 to 1.09)	0.27

High use is defined as >12 actuations per 24-hours of budesonide/formoterol for SMART and >16 actuations per 24-hours of salbutamol for Standard.*: Sensitivity analysis, using a modified definition of a high use episode for the Standard group, to adjust for the use of budesonide/formoterol in excess of the four maintenance actuations by some participants on occasions.

6.10 Number of days of high use

The SMART regimen was associated with significantly fewer high use days (Table 6.6).

Table 6.6: High use days and high use days without medical review

Outcome	SMART group (N = 151)	Standard group (N = 152)	Relative Rate SMART vs Standard (95% CI)	P value
High use days				
Number of days of high use	5.1±14.3	8.9±20.9	0.58 (0.39 to 0.88)	0.01
Number of days of high use in participants with at least one high use episode*	9.1±18.2	19.9±27.7	-	-
High use days without medical review				
Number of days of high use without medical review in participants with at least one high use episode*	8.5±17.8	18.3±24.8	0.49 (0.31 to 0.75)	0.001

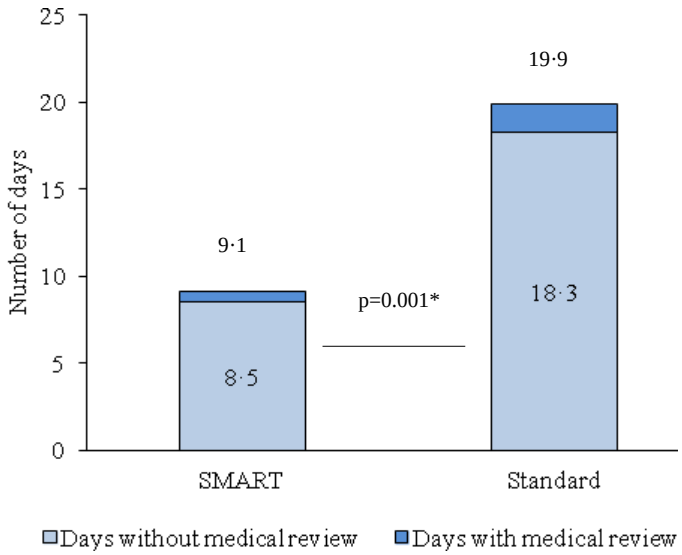
Plus-minus values are means ± SD.
High use is defined as >12 actuations per 24-hours of budesonide/formoterol for SMART and >16 actuations per 24-hours of salbutamol for Standard.
Estimates are weighted as part of the analysis and may be numerically different to the values calculated from the tabulated mean values.
Analysis of the relative rates of days of overuse was calculated by Poisson regression with an offset for the treatment exposure. The analysis suggested over-dispersion and a dispersion term was used to adjust for the over-dispersion.
*: n=84 for SMART and n=68 for Standard.

6.11 Number of days of high use without medical review

In participants who had at least one high use episode, there were significantly fewer days of high use without medical review in the SMART group (Table 6.6).

The proportion of high use days that were without medical review were 8.5/9.1 days (93.4%) in the SMART group and 18.3/19.9 days (92.0%) in the Standard group (Table 6.6 and Figure 6.5).

Figure 6.5: Number of days of high use in participants with at least one high use episode



*refers to the comparison of days of high use without medical review

6.12 Marked overuse

The risk of at least one marked overuse episode was similar between groups (Table 6.7). The number of days with marked overuse was significantly less for the SMART group (Table 6.7).

6.13 Number of days of marked overuse without medical review

In participants who had at least one marked overuse episode, the number of days of marked overuse without medical review was not significantly different between the groups (Table 6.7).

The proportion of marked overuse days that were without medical review were 6.7/7.4 days (90.5%) in the SMART group and 11.7/13.1 days (89.3%) in the Standard group (Table 6.7).

Table 6.7: Marked overuse days and marked overuse without medical review

Outcome	SMART group (N = 151)	Standard group (N = 152)	Relative Risk or Rate SMART vs Standard (95% CI)	P value
Marked overuse				
At least one episode of marked overuse, n (%)	54 (35.8)	56 (36.8)	0.97 (0.72 to 1.31)	0.85
Number of days of marked overuse	2.6±10.2	4.8±14.9	0.56 (0.35 to 0.88)	0.013
Number of days of marked overuse in participants with at least one marked overuse episode*	7.4±16.0	13.1±22.3	-	-
Marked overuse without medical review				
Number of days of marked overuse without medical review in participants with at least one marked overuse episode*	6.7±15.7	11.7±19.0	0.62 (0.37 to 1.06)	0.079

Plus-minus values are means ± SD.
Marked overuse is defined as >16 actuations per 24-hours of budesonide/formoterol for SMART and >24 actuations per 24-hours of salbutamol for Standard.
Estimates are weighted as part of the analysis and may be numerically different to the values calculated from the tabulated mean values.
Analysis of the relative rates of days of overuse was calculated by Poisson regression with an offset for the treatment exposure. The analysis suggested over-dispersion and a dispersion term was used to adjust for the over-dispersion.
*: n=54 for SMART and n=56 for Standard.

6.14 Extreme overuse

The risk of at least one extreme overuse episode was similar between groups (Table 6.8). The number of days with extreme overuse was significantly less for the SMART group (Table 6.8).

6.15 Number of days of extreme overuse without medical review

In participants who had at least one extreme overuse episode, the number of days of extreme overuse without medical review was not significantly different between the groups (Table 6.8).

The proportion of extreme overuse days that were without medical review were 5.2/5.8 days (89.7%) in the SMART group and 9.6/11.0 days (87.3%) in the Standard group (Table 6.8).

Table 6.8: Extreme overuse days and extreme overuse without medical review

Outcome	SMART group (N = 151)	Standard group (N = 152)	Relative Risk or Rate SMART vs Standard (95% CI)	P value
Extreme overuse				
At least one episode of extreme overuse, no. (%)	41 (27.2)	40 (26.3)	1.03 (0.71 to 1.50)	0.87
Number of days of extreme overuse	1.6±6.7	2.9±12.2	0.56 (0.34 to 0.91)	0.02
Number of days of extreme overuse in participants with at least one extreme overuse episode*	5.8±11.9	11.0±22.1	-	-
Extreme overuse without medical review				
Number of days of extreme overuse without medical review in participants with at least one extreme overuse episode*	5.2±11.9	9.6±18.3	0.59 (0.31 to 1.10)	0.096

Plus-minus values are means ± SD.
Extreme overuse is defined as >20 actuations per 24-hours of budesonide/formoterol for SMART and >32 actuations per 24-hours of salbutamol for Standard.
Estimates are weighted as part of the analysis and may be numerically different to the values calculated from the tabulated mean values.
Analysis of the relative rates of days of overuse was calculated by Poisson regression with an offset for the treatment exposure. The analysis suggested over-dispersion and a dispersion term was used to adjust for the over-dispersion.
*: n=41 for SMART and n=40 for Standard.

6.16 Underuse of maintenance budesonide/formoterol treatment

Most participants had at least one episode of underuse (Table 6.9). The number of days with ≤1 actuations was not significantly different between the two regimens (Table 6.9).

There were significantly fewer days with zero actuations (non-adherence) in the SMART group (Table 6.9).

Table 6.9: Underuse of maintenance budesonide/formoterol treatment

Outcome	SMART group (N = 151)	Standard group (N = 152)	Relative Risk or Rate SMART vs Standard (95% CI)	P value
At least one day with zero actuations, n (%)	120 (79.5)	126 (82.9)	0.96 (0.86 to 1.07)	0.45
Number of days with zero actuations	23.9±32.6	33.6±42.8	0.72 (0.55 to 0.95)	0.022
At least one day with one or zero actuations, n (%)	129 (85.4)	132 (86.8)	0.98 (0.90 to 1.08)	0.72
Number of days with one or zero actuations	28.8±35.4	36.9±44.6	0.80 (0.62 to 1.03)	0.087
At least one day with two or less actuations, n (%)	143 (94.7)	150 (98.7)	0.96 (0.92 to 1.00)	0.052
Number of days with two or less actuations	61.3±47.4	70.6±51.0	0.89 (0.76 to 1.05)	0.19

Plus/minus values are mean ± SD.
Estimates are weighted as part of the analysis and may be numerically different to the values calculated from the tabulated mean values.
Analysis of the relative rates of days of underuse was calculated by Poisson regression with an offset of the logarithm of the treatment exposure. The variable days of underuse was over-dispersed and a deviance-based over-dispersion correction term was used in the Poisson regression.

6.17 Corticosteroid load

6.17.1 Daily ICS dose

Participants randomised to the SMART regimen had a significantly greater mean exposure to budesonide of 259.2µg per day (Table 6.10).

The distribution of mean daily budesonide dose is shown in Figures 6.6 and 6.7. 25/151 (16.6%) and 32/152 (23.0%) participants in the SMART and Standard groups respectively had mean daily budesonide doses of less than 400µg per day. 64/151 (42.4%) participants in the SMART group and 40/152 (26.3%) participants in the Standard group had mean daily budesonide doses greater than 800µg per day (Figures 6.6 and 6.7).

6.17.2 Oral corticosteroid dose

Participants randomised to the SMART regimen had a significantly lower mean exposure to prednisone of 49.1mg over the study period (Table 6.10) and had significantly fewer courses of oral prednisone per year of follow-up (Table 6.10).

Table 6.10: ICS dose, oral corticosteroid dose and composite systemic corticosteroid exposure

Outcome	SMART group (N = 151)	Standard group (N = 152)	Relative Risk or Rate SMART vs Standard (95% CI)	P value
Daily ICS dose *				
Daily budesonide dose, µg	943.5±1502.5	684.3±390.5	1.22 (1.06 to 1.41) †	0.006
Oral corticosteroid dose ‡				
Oral corticosteroid dose, mg prednisone	77.5±240.5	126.6±382.1		0.011 §
Number of courses of oral corticosteroids per year of follow-up ‖	0.80±2.5	1.1±1.9	0.58 (0.41 to 0.84)	0.004
Composite systemic corticosteroid exposure (ICS plus oral) ¶				
Composite systemic corticosteroid exposure, mg prednisone equivalent per year	793.7±893.1	772.1±1062.7	1.03 (0.86 to 1.22) †	0.76

Plus/minus values are mean ± SD. *: The logarithm of the annualised ICS use was the response variable in a weighted normal linear model, with the randomised treatment as a predictor and the treatment exposure time as a weight (individuals with longer periods of treatment exposure were given more weight and those with shorter periods of treatment exposure less weight in the analysis). n=150 for SMART and n=151 for Standard (logarithm zero cannot be defined and therefore one participant in each group, whose measured ICS dose was zero, was not included in the analysis). The SMART participant had a treatment exposure period of one day prior to discontinuation and the Standard participant discontinued immediately after the first study visit. †: Ratio of mean values of annualised corticosteroid use (Exponent of the difference in logarithms of SMART minus Standard). ‡: One Standard patient self-administered an overdose of 800mg prednisone per day for 5 days for asthma (sensitivity analysis for oral corticosteroid dose with this participant excluded from the data is shown in Table 6.11). Corticosteroid conversion: 100mg intravenous hydrocortisone:25mg oral prednisone. §: Chi-squared 11·1, degrees of freedom 3 (bands for contingency tables: 0, 0-200, 200-400, 400+). ‖: n=151 for Standard due to one participant who discontinued immediately after the first study visit. ¶: Budesonide dose per year was converted to prednisone-equivalent dose (5000µg inhaled budesonide=10mg oral prednisone). The annualised systemic corticosteroid exposure was the sum of the prednisone-equivalent dose per year and the oral corticosteroid dose per year. The logarithm of the annualised systemic corticosteroid exposure was the response variable in a weighted normal linear model, with the randomised treatment as a predictor and the period of observation as a weight (individuals with longer periods of observation were given more weight and those with shorter periods of observation less weight in the analysis). n=150 for SMART and n=151 for Standard (logarithm zero cannot be defined and therefore one participant in each group, whose measured ICS and prednisone dose was zero, was not included in the analysis).

Figure 6.6: Mean daily budesonide dose for the SMART group

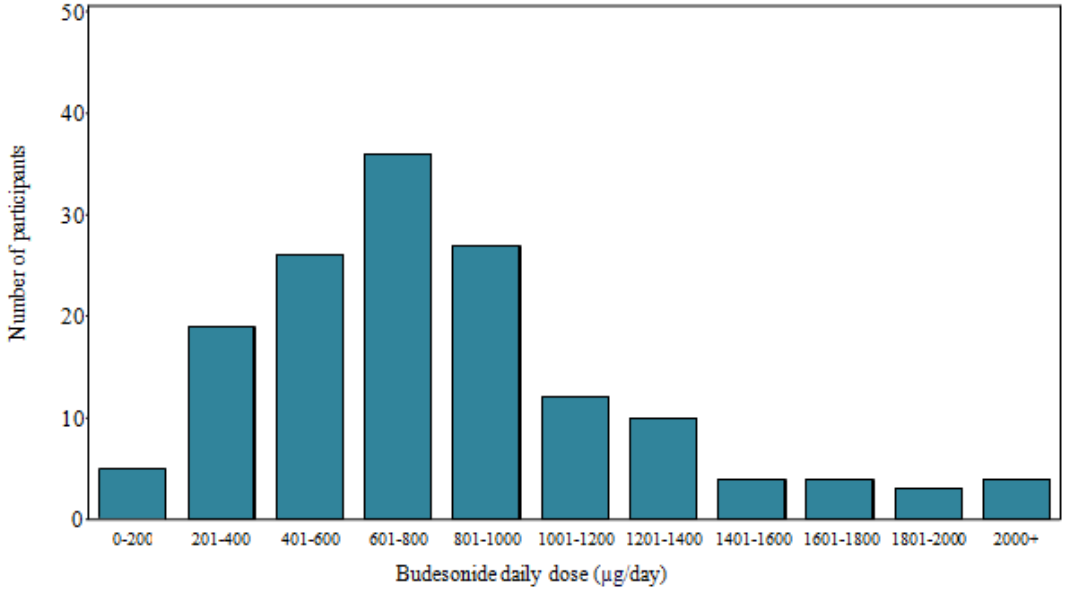
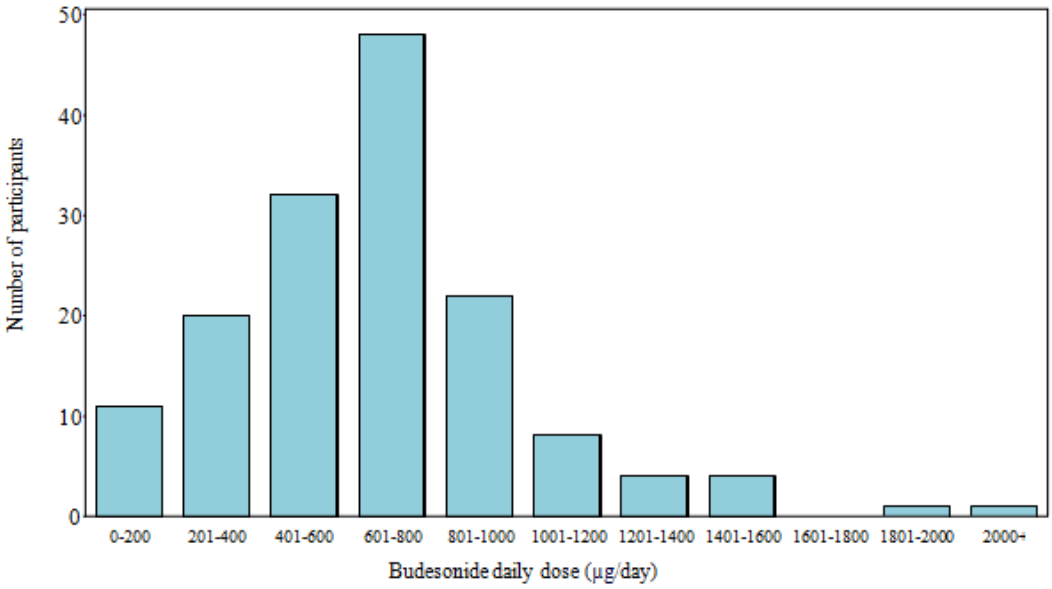


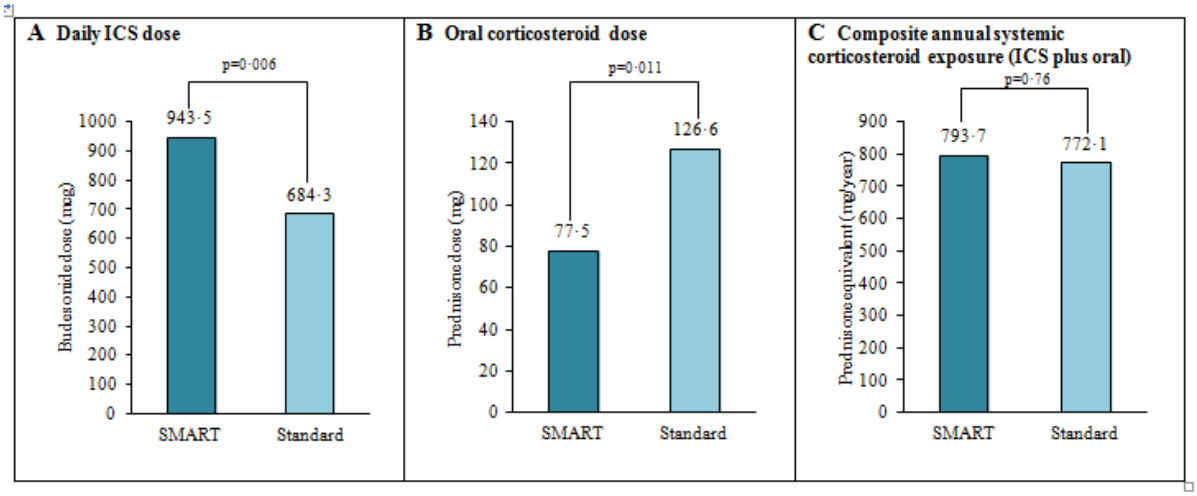
Figure 6.7: Mean daily budesonide dose for the Standard group



6.17.3 Composite systemic corticosteroid exposure

Overall composite annual systemic corticosteroid exposure was similar between the two treatment groups (Table 6.10 and Figure 6.8).

Figure 6.8: Corticosteroid exposure



Daily ICS dose (Panel A), oral corticosteriod dose (Panel B) and composite annual systemic corticosteriod exposure (Panel C). ICS: Inhaled corticosteroid.

6.17.4 Sensitivity analysis with one Standard participant removed from the analyses of oral corticosteroid dose and composite systemic corticosteroid exposure

One participant in the Standard group self-administered an overdose of 800mg prednisone per day for five days for asthma. A sensitivity analysis was performed for the analyses of oral corticosteroid dose and composite systemic corticosteroid exposure, with this participant excluded from the data (Table 6.11). The results of these analyses supported the intention to treat analyses.

Table 6.11: Sensitivity analyses with one Standard participant removed from the analyses of oral corticosteroid dose and composite systemic corticosteroid exposure

Outcome	SMART group (N = 151)	Standard group (N = 151)	P value
Oral corticosteroid dose			
Sensitivity analysis of oral corticosteroid dose, mg prednisone	77.5±240.5	99.9±194.5	0.011*
Composite systemic corticosteroid exposure (ICS plus oral)			
Sensitivity analysis of composite systemic corticosteroid exposure, mg prednisone equivalent per year	793.7±893.1	696.9±525.8	0.62 †

Plus/minus values are mean ± SD.* Chi-squared 11.1, degrees of freedom 3 (bands for contingency tables: 0, 0-200, 200-400, 400+). P value to 3 figures is 0.0114. † The ratio of mean values (95% CI) of annualised systemic corticosteroid exposure [Exponent of the difference in logarithms of SMART minus Standard], was 1.04 (0.88 to 1.23). N=150 for SMART (logarithm zero cannot be defined and therefore one participant, who had measured ICS and prednisone doses of zero, was not included in the analysis. This participant had a treatment exposure period of one day prior to discontinuation) and N=150 for Standard (logarithm zero cannot be defined and therefore one participant, who had measured ICS and prednisone doses of zero, was not included in the analysis. This participant discontinued immediately after the first study visit). The P value to 3 figures for the oral corticosteroid dose sensitivity analysis is 0.0114. The P value to 3 figures for the oral corticosteroid dose intention to treat analysis (i.e. with the outlier participant included in the dataset) is 0.0112. The apparent discrepancy between the large change in mean values for oral corticosteroid dose and much smaller change in P values is because only one outlying participant is taken from the fourth band of the contingency table and so had virtually no influence on the contingency table analysis.

6.18 Severe asthma exacerbations

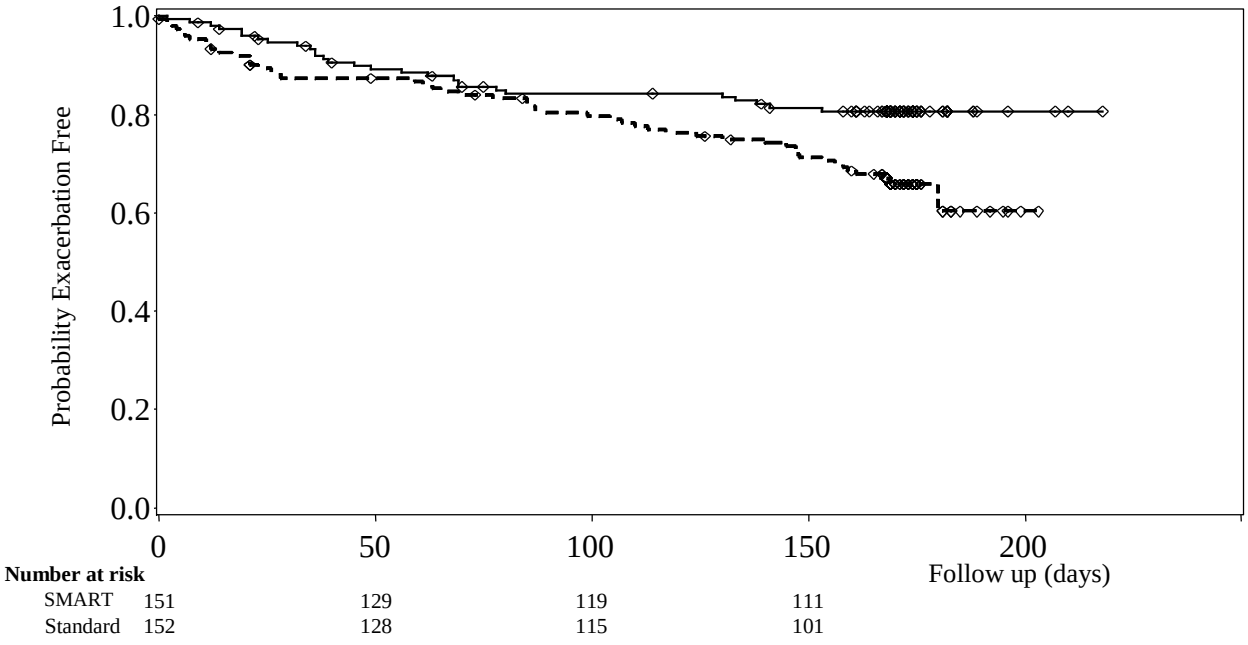
The SMART regimen was associated with significantly fewer severe exacerbations (Table 6.12). The Hazard ratio for the time to first severe asthma exacerbation was significantly less for the SMART group (Figure 6.9). 225 participants had no severe exacerbations, 62 had one severe exacerbation and 16 had two or more severe exacerbations.

Table 6.12: Severe asthma exacerbations

Outcome	SMART group (N = 151)	Standard group (N = 152)	Relative Risk or Rate SMART vs Standard (95% CI)	P value
Severe asthma exacerbations *				
Participants with at least one severe exacerbation, n (%)	28 (18.5)	50 (32.9)	0.56 (0.38 to 0.84)	0.004
Number of severe exacerbations, (weighted mean rate per year)	35 (0.53)	66 (0.97)	0.54 (0.36 to 0.82)	0.004

Estimates are weighted as part of the analysis and may be numerically different to the values calculated from the tabulated mean values.
The weighted mean rate per year is the total number of events in the study group divided by the total person follow-up time in years for the study group.
Relative rates were calculated by Poisson regression with an offset of the logarithm of the period of observation (for the analyses of severe exacerbation).
*: A severe exacerbation is defined as the use of systemic corticosteroids for at least 3 days or a hospitalisation or ED visit because of asthma, requiring systemic corticosteroids. Courses of corticosteroids separated by 7 days or more were treated as separate severe exacerbations.

Figure 6.9: Kaplan-Meier plots of time to first severe asthma exacerbation



Hazard ratio (95% CI) for time to first severe asthma exacerbation, SMART versus Standard: 0.53 (0.33 to 0.84), P=0.008.

Symbol: Censored values; Continuous line: SMART group; Dashed line: Standard group.

6.19 Hospital admissions and ED attendances for asthma

There was no difference in the risk of a hospital admission or hospital attendance (hospital admission and/or ED attendance) for asthma between the groups (Table 6.13). The number of hospital admissions or hospital attendances (hospital admission and/or ED attendance) for asthma was similar between the groups (Table 6.13).

Table 6.13: Hospital admissions and ED attendances for asthma

Outcome	SMART group (N = 151)	Standard group (N = 152)	Relative Risk or Rate SMART vs Standard (95% CI)	P value
Hospital and ED attendances for asthma				
Participants with at least one hospital admission or ED attendance, n (%)	7 (4.6)	9 (5.9)	0.78 (0.30 to 2.05)	0.62
Number of hospital admissions and/or ED attendances, (weighted mean rate per year)	10 (0.15)	12 (0.18)	0.85 (0.37 to 2.00)	0.71
Hospital admissions for asthma				
Participants with at least one hospital admission, n (%)	2 (1.3)	2 (1.3)	1.01 (0.14 to 7.05)	0.99
Number of hospital admissions, (weighted mean rate per year)	3 (0.05)	2 (0.03)	1.54 (0.26 to 9.09)	0.91

Estimates are weighted as part of the analysis and may be numerically different to the values calculated from the tabulated mean values.
The weighted mean rate per year is the total number of events in the study group divided by the total person follow-up time in years for the study group.
Relative rates were calculated by Poisson regression with an offset of the logarithm of the period of observation (for the analyses of hospital admission and ED attendance).

6.20 Asthma control

There was a marked reduction in ACQ-7 score in both groups (Table 6.14 and Figure 6.10). There was a significant treatment by time interaction term for ACQ-7 (p=0·02) and the pair-wise comparisons between treatments at each measurement time suggested the ACQ-7 was significantly lower in the SMART group at the fourth visit but not the other visits (Table 6.14).

62/135 (45.9%) participants in the SMART group and 50/142 (35.2%) participants in the Standard group had an ACQ-7 score of ≤0.75 at six months (Visit 5). 31/135 (23.0%) participants in the SMART group and 39/142 (27.5%) participants in the Standard group had an ACQ-7 score of ≥1.5 at six months.

Table 6.14: Asthma control by ACQ-7 score

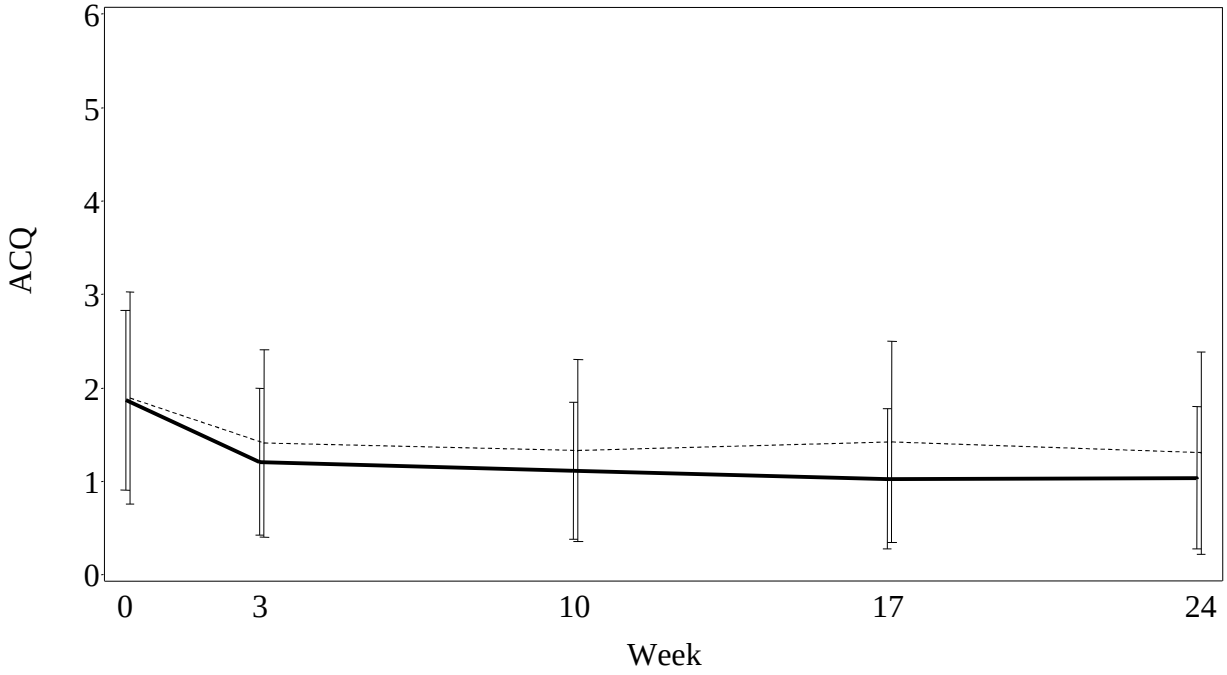
Visit	SMART group (N = 151)	Standard group (N = 152)	SMART minus Standard (95% CI)	P value
ACQ-7 *				
Visit 1	1.87±0.96	1.90±1.13	-	-
Visit 2	1.21±0.79	1.41±1.01	-0.20 (-0.40 to 0.01)	0.058
Visit 3	1.12±0.73	1.33±0.97	-0.19 (-0.39 to 0.01)	0.063
Visit 4	1.02±0.75	1.42±1.08	-0.36 (-0.58 to -0.15)	0.001
Visit 5	1.04±0.76	1.30±1.08	-0.20 (-0.42 to 0.02)	0.08

Plus/minus values are mean ± SD. *: ACQ-7 score is a composite score of asthma control, comprising questions on asthma symptoms, rescue bronchodilator use and FEV_1 % predicted (overall scores range from 0 to 6, with scores ≤0.75 suggesting 'well-controlled' asthma and scores ≥1.50 suggesting 'not well-controlled' asthma). The minimal clinically important difference for ACQ-7 score is 0.5.

ACQ-7 was analysed by mixed linear model examining response profiles at each time point using random effects for individual subjects and an unstructured covariance pattern to account for correlation between measurements on the same subjects (this model forces a common intercept and adjusts for baseline values in this way). P-value for treatment by time interaction term was statistically significant, p=0.02, consistent with the difference between SMART and Standard being different at different times.

Visit 2: SMART: n=150, Standard: n=150; Visit 3: SMART: n=143, Standard: n=147; Visit 4: SMART: n=139, Standard: n=141; Visit 5: SMART: n=135, Standard: n=142.

Figure 6.10: Asthma control over the study period



Plot of mean ACQ-7 score ± 1 SD by time. Solid line is SMART, dashed line is Standard.

6.21 Lung function

Lung function measurements (FEV_1 or FEV_1 % predicted) were similar between the groups at all visits (Table 6.15 and Figure 6.11).

The p-value for the treatment by time interaction term was not statistically significant (p=0·51), meaning that there was no evidence that the difference between SMART and Standard was different at different measurement times, for both FEV_1 and FEV_1 % predicted. The overall effect of treatment averaged over all measurement times for FEV_1 was also not statistically significant: SMART minus Standard (95% CI) 0.12 L (-0.07 to 0.31), p=0.23. The overall effect of treatment averaged over all measurement times for FEV_1 % predicted was also not statistically significant: SMART minus Standard (95% CI) 1.5% (-2.6 to 5.6), p=0.47.

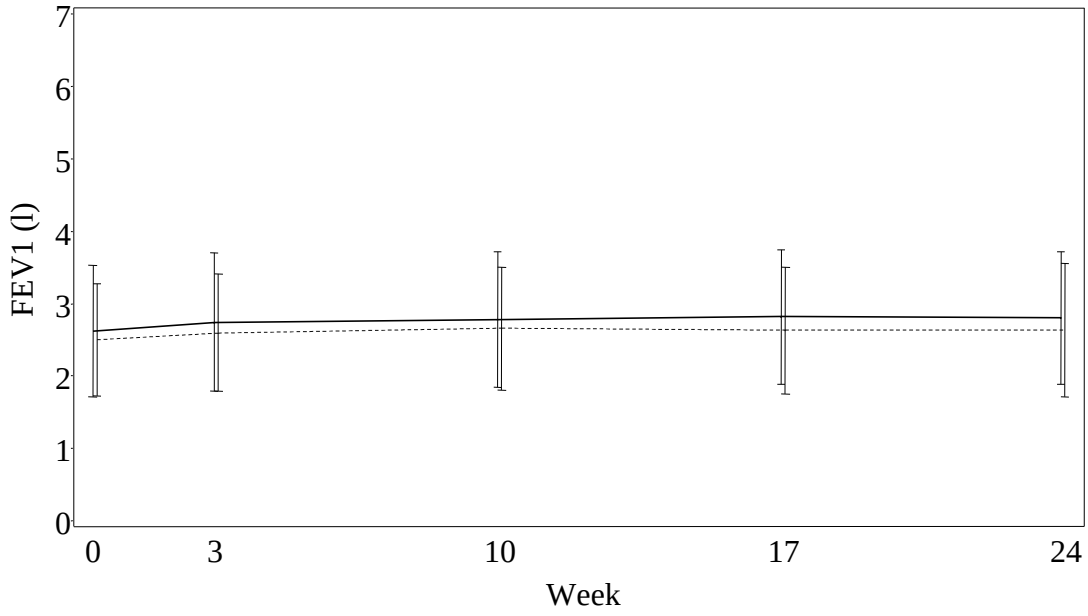
Table 6.15: Lung function results

Outcome	SMART group (N = 151)	Standard group (N = 152)	SMART minus Standard (95% CI)	P value
FEV_1 (Litres) *				
Visit 1	2.62±0.91	2.50±0.78		
Visit 5	2.80±0.91	2.64±0.93	0.15	0.16
			(-0.06 to 0.36)	
FEV_1 % predicted *				
Visit 1	81.6±18.9	80.4±20.5		
Visit 5	87.1±17.0	84.1±22.0	2.5	0.28
			(-2.0 to 7.0)	

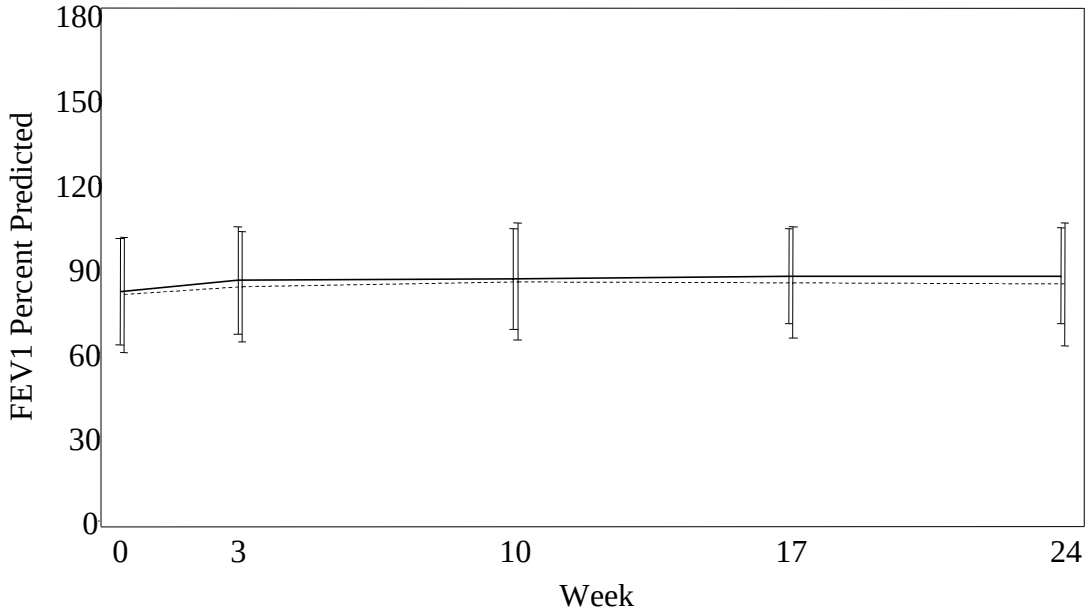
Plus/minus values are mean ± SD. * FEV_1 and FEV_1 % predicted were analysed by mixed linear model examining response profiles at each time point using random effects for individual subjects and an unstructured covariance pattern to account for correlation between measurements on the same subjects (this model forces a common intercept and adjusts for baseline values in this way). P-value for the treatment by time interaction term was not statistically significant (p=0.51). Visit 5: SMART: n=133, Standard: n=141.

Figure 6.11: Lung function

A: FEV_1



B: FEV_1 % predicted



Plot of mean FEV_1 (Panel A) and mean FEV_1% predicted (Panel B) ± 1 SD by time.
Solid line is SMART, dashed line is Standard.

6.22 Satisfaction with inhaled asthma treatment (SATQ)

Ease of use of medication scores were significantly higher in the SMART group at the end of the study (Table 6.16). Domain scores for effectiveness of medication, burden of medication, side effects and the overall SATQ score were similar between groups (Table 6.16).

6.23 Adverse events

The adverse events were similar between treatment groups and are detailed in full in Appendix H. The most frequently occurring adverse events were upper respiratory tract infection [SMART 66/151 (44%) and Standard 65/152 (43%) participants], injury/trauma/musculoskeletal ailment [SMART 27/151 (18%) and Standard 17/152 (11%) participants] and adverse taste [SMART 19/151 (13%) and Standard 19/152 (13%) participants].

17/151 (11.3%) of participants in the SMART group and 11/152 (7.2%) of participants in the Standard group discontinued study treatment. Discontinuations due to adverse events are shown in Table 6.17.

Table 6.16: SATQ results

Domain	SMART group (N = 151)	Standard group (N = 152)	SMART minus Standard (95% CI)	P value
Effectiveness of treatment				
Visit 1	5.0±1.2	4.9±1.3		
Visit 5	6.1±1.2	6.1±1.0	0.04	0.73
			(-0.29 to 0.20)	
Ease of use of medication				
Visit 1	5.4±1.2	5.4±1.2		
Visit 5	6.2±0.9	6.0±1.0	0.23	0.021
			(0.03 to 0.42)	
Burden of asthma medication				
Visit 1	4.5±1.3	4.6±1.4		
Visit 5	5.0±1.1	5.1±1.2	-0.04	0.73
			(-0.27 to 0.19)	
Side effects and worries				
Visit 1	4.6±1.2	4.7±1.3		
Visit 5	5.0±1.2	5.2±1.2	-0.13	0.32
			(-0.40 to 0.13)	
Overall score				
Visit 1	4.9±0.9	4.9±1.0		
Visit 5	5.6±0.8	5.6±0.9	-0.002	0.98
			(-0.18 to 0.17)	

Plus/minus values are mean ± SD. The SATQ is a questionnaire used to measure patients' satisfaction with their inhaled asthma treatment (Campbell et al., 2003). The questionnaire comprised 26 questions, divided into four domains: effectiveness of medication (8 questions); ease of use (7 questions); burden of asthma medication (6 questions); and side effects and worries (5 questions). Each question was scored on a scale of 1 to 7. Negatively phrased questions were reversed for analysis. Domain scores were calculated as the average of the responses for that domain, with higher values indicating greater satisfaction with treatment (range 1 to 7). The total overall score was calculated as the mean of the four domain scores. The minimum clinically important difference for the SATQ has not been defined. SATQ was analysed by ANCOVA with the Visit 1 value as a baseline covariate, to give an adjusted treatment difference for SMART minus Standard. Visit 5: SMART: n=144, Standard: n=150.

Table 6.17: Discontinuation due to adverse events

	SMART (N = 151)		Standard (N = 152)	
Adverse event	**Number of participants**	**%**	**Number of participants**	**%**
Palpitations	1	0.7	2	1.3
Headache	1	0.7	0	0
Voice change	0	0.0	1	0.7
Mucous in throat	0	0.0	1	0.7
Diarrhoea, vomiting and medication taste	0	0.0	1	0.7
Medication taste, dry throat and voice change	1	0.7	0	0.0

6.24 Serious adverse events

There were no deaths, or asthma-related intensive care unit admissions or intubations. No participants required assisted ventilation (e.g. CPAP or NIV). All serious adverse events, eight in the SMART group and seven in Standard group, were considered by their treating physicians to be unrelated to study participation (Table 6.18).

Table 6.18: Serious adverse events

	SMART (N = 151)		Standard (N = 152)	
Serious adverse event	**Number of participants**	**%**	**Number of participants**	**%**
Hospital admission for asthma*	2	1.3	2	1.3
Cellulitis	0	0.0	3	2.0
Heart failure secondary to idiopathic dilated cardiomyopathy †	1	0.7	0	0.0
Non-cardiac chest pain, self-limiting	1	0.7	0	0.0
Metabolic derangement due to self-administered prednisone overdose	0	0.0	1	0.7
Calf myositis	0	0.0	1	0.7
Pneumonia	1	0.7	0	0.0
Frozen shoulder	1	0.7	0	0.0
Missed miscarriage requiring hospital admission	1	0.7	0	0.0

*: one SMART participant had 2 hospital admissions for asthma †: Symptoms pre-dated enrollment

6.25 Pregnancy in study participants

Four participants in the SMART group and five in the Standard group were pregnant during study participation. The outcomes for each pregnancy are detailed in Table 6.19.

Table 6.19: Pregnancy in study participants

Study group	Pregnant at study entry	Outcome	Detail
Standard	Yes	Healthy baby delivered	
Standard	No	Healthy baby delivered	
Standard	No	Healthy baby delivered	
Standard	No	Healthy baby delivered	
Standard	No	Miscarriage in early pregnancy	Miscarriage after study completion
SMART	No	Miscarriage in early pregnancy	Continued study participation
SMART	No	Miscarriage in early pregnancy	Continued study participation
SMART	No	Healthy baby delivered	
SMART	Yes	Healthy baby delivered	

6.26 Dose dumping database search

A similar number of participants in both groups, 2/151 (1.3%) participants in the SMART group and 5/152 (3.3%) participants in the Standard group, met the dose dumping criteria applied to the dataset in which actuation data on study visit days were removed (Table 6.20). Dose dumping days were observed infrequently in both groups (Table 6.20).

The number of participants with at least one episode of dose dumping and the number of days meeting dose dumping criteria increased when the dataset in which actuation data on study visit days were included was used (Table 6.21).

Table 6.20: Dose dumping in which actuation data on study visit days were removed from the dataset*

Outcome	SMART (N = 151)	Standard (N = 152)
Participants with at least one episode of dose dumping, n (%) †	2 (1.3)	5 (3.3)
Number of days of dose dumping	2	7

* The dose dumping criteria used was ≥100 actuations occurring within ≤3 hours (Rand et al., 1992) in the dataset in which actuations on study visit days were removed. For the SMART group, this was the number of days meeting dose dumping criteria with budesonide/formoterol inhalers; for the Standard group, this was the number of days meeting dose dumping criteria with salbutamol inhalers.
† In all of these participants, high use not meeting dose dumping criteria was observed on at least one other day during study participation.

Table 6.21: Dose dumping in which actuation data on study visit days were included in the dataset*

Outcome	SMART (N = 151)	Standard (N = 152)
Participants with at least one episode of dose dumping, n (%)	3 (2.0)	6 (3.9)
Number of days of dose dumping	5	8

* The dose dumping criteria used was ≥100 actuations occurring within ≤3 hours (Rand et al., 1992) in the dataset in which actuations on study visit days were included. For the SMART group, this was the number of days meeting dose dumping criteria with budesonide/formoterol inhalers; for the Standard group, this was the number of days meeting dose dumping criteria with salbutamol inhalers.

Chapter Seven: Discussion

7.1 The SMART study randomised controlled trial findings

This study demonstrates that combination budesonide/formoterol inhaler therapy prescribed according to the SMART regimen has a favourable safety and efficacy profile compared to the Standard regimen of maintenance budesonide/formoterol inhaler therapy and salbutamol as reliever in adult asthma patients at risk of severe exacerbations. The SMART regimen reduces the risk of severe asthma exacerbations without increasing the risk of beta-agonist overuse without medical review or increasing the long-term systemic corticosteroid burden. Although no significant difference was found between groups in the risk of at least one high beta-agonist use episode, the number of days with high use, marked overuse and extreme overuse were approximately 40% lower in patients randomised to the SMART regimen. The number of high use days without medical review was significantly lower in the SMART group, although when an overuse episode occurred, the likelihood of a patient seeking medical review was similar between groups. This suggests that the increasing use of budesonide/formoterol during worsening asthma with the SMART regimen does not lead to greater delay in seeking medical help. This observation is important, as delay in seeking medical assistance in the setting of severe exacerbations is one of the most important factors contributing to a fatal outcome (Fraser et al., 1971). Patients treated with the SMART regimen experienced

46% fewer severe asthma exacerbations, similar to previous studies in moderate to severe asthma (Cates and Lasserson, 2009; Rabe et al., 2006a; O'Byrne et al., 2005).

Asthma patients prescribed the SMART regimen had a greater mean daily ICS exposure. However, due to the reduction in severe exacerbations, the SMART group had a lower oral corticosteroid exposure, with a similar overall systemic corticosteroid burden between the two regimens. Our data also inform the debate regarding the potential mechanisms by which use of the SMART regimen reduces severe asthma exacerbations. Patients in both treatment groups underused their maintenance budesonide/formoterol therapy, but the SMART group had fewer days of non-adherence, on which no maintenance therapy was taken. This reduction in non-adherence may contribute to reducing the risk of severe exacerbations, together with the self-titrated escalation of budesonide/formoterol use in response to worsening asthma (Sovani et al., 2008; Barnes, 2007). In support of this latter mechanism, the frequent use of ICS, such as that self-administered by patients in the SMART group on days of high, marked and extreme overuse, has substantial efficacy in the treatment of acute severe asthma (Rodrigo, 2006).

This was a study of patients at risk of severe asthma exacerbations (O'Connor et al., 2010), 90% of whom had at least one severe exacerbation, and 40% of whom had two or more severe exacerbations, in the preceding year. Around one in four patients self-administered >32 actuations per day of salbutamol (or equivalent) on at least one occasion during the study. Furthermore, in patients with a high use episode, approximately 90% of high use days occurred without medical review within the next 48 hours, despite this advice documented in the asthma self-management plans

provided. These findings illustrate the extent of unsupervised beta-agonist overuse by patients at risk of severe asthma exacerbations.

Beta-agonist overuse was used as an indirect measure of risk of mortality (Abramson et al., 2001; Eisner et al., 2001; Suissa et al., 1994; Spitzer et al., 1992). In consideration of this risk, there is a concern that because formoterol has greater intrinsic activity than salbutamol (Hanania et al., 2002), it could potentially result in greater maximum adverse effects in the situation of beta-agonist overuse. This pharmacological property is common to both isoprenaline and fenoterol (Hanania et al., 2002), of which the high-dose preparations have been implicated in epidemics of asthma mortality (Crane et al., 1989; Stolley and Schinnar, 1978). The reduction in both overuse episodes and severe exacerbations (Crane et al., 1992) with the SMART regimen, together with the previously reported reduction in ED visits or hospital admissions (Rabe et al., 2006a), may indicate an accompanying reduced risk of mortality. However, this interpretation comes with the caveat that this study and the SMART clinical trial programme (Sears and Radner, 2009) have insufficient power to rule out an effect on asthma mortality risk, and further study of this issue is required.

In this study, asthma control over six months improved markedly in both groups, in excess of the 0.5 points considered to be a clinically important improvement in ACQ-7 score (Juniper et al., 1999). The reductions (improvements) in ACQ-7 scores were similar for three of four visits between the SMART and Standard groups. Regarding other patient reported outcomes, improvements in overall satisfaction scores for inhaled treatment were similar between groups. However, patients treated

with the SMART regimen had greater improvements in the ease of treatment use domain of the SATQ. Considered together, these data suggest that the use of the SMART regimen achieves at least comparable improvements in asthma control compared to Standard therapy (Bateman et al., 2010) and that patients regard this treatment as acceptable for use in clinical practice.

In the Standard group, 21% of patients used less than 400µg of budesonide per day on average throughout the study period, with 26% of the group using more than the prescribed maintenance dose of 800µg per day. These findings complement the previous observation that patients prescribed a different combination ICS/LABA inhaler (fluticasone/salmeterol) as fixed-dose maintenance treatment may vary their use of treatment according to perceived need (Perrin et al., 2010). These different patterns of use may also apply to fixed-dose therapy with other combination ICS/LABA inhalers.

In summary, this study has demonstrated that in asthma patients at risk of severe exacerbations, combination budesonide/formoterol therapy prescribed according to the SMART regimen has a favourable risk/benefit profile compared to Standard maintenance therapy. The SMART regimen may be considered as the preferred approach in asthma patients at BTS Steps 2, 3 or 4 (SIGN/BTS, 2012) who are at risk of severe exacerbations.

7.2 Strengths of the study

7.2.1 Real-world study design

A number of design features allowed the study to enrol patients representative of those seen in clinical practice. Recruitment occurred from both community and hospital settings, in order to enrol a heterogeneous group of patients. The trial was conducted in both primary and secondary care, to allow improved accessibility to the study. Inclusion/exclusion criteria were broad, to enable the inclusion of patients with asthma and co-existing conditions. Patients at risk of poor adherence or beta-agonist overuse were eligible and there was no upper limit for pre-study ICS dose. Finally, day-to-day asthma care remained with the patient's primary care physician, reflecting real-world clinical practice.

These features are consistent with key recommendations regarding the importance of conducting real-world 'effectiveness' research (Holgate, 2012; Krishnan, Schatz and Apter, 2011; Lieu et al., 2011; Ware and Hamel, 2011).

7.2.2 Monitor performance

Validated electronic monitors were used with extensive trial quality control processes, as the optimal method to measure actual use of medication. This allowed assessment of the potential risks associated with high doses of ICS and beta-agonist with both short-term and cumulative exposure. This study has shown that the Smartinhaler Tracker is a highly reliable monitor of MDI use by patients and that

implementing an extensive pre- and within-trial monitor and data checking process can help to safeguard data acquisition (Bender, 2013).

In pre-trial checks, 98% of monitors were found to be fully functional and ready for patient use. The pre-trial checks identified a minority of malfunctioning devices that required repair prior to dispensing, highlighting the importance of investigator-led post-production testing of monitor function. The within-trial checking process allowed monitors damaged by participant use to be identified and removed from circulation, thus reducing the occurrence of data loss as a result of device malfunction. The rate of complete data loss due to missing monitors was 3.5% (93 of 2642 monitors), whereas data loss due to monitor malfunction in returned devices was 1.9% (51 of 2642 monitors). Using systems incorporated into the software used for monitor upload, data which was potentially corrupted was identified and prevented from database entry.

Complete data was available from 2498/2642 (94.5%) of the monitors dispensed to patients in this trial. Of the 144 monitors from which there was missing data, approximately two-thirds (93/144) were lost or thrown away by participants in this real-world study, despite repeated advice to the contrary. Thus, complete data in 2498/2549 (98.0%) of returned monitors was present. In the remaining 51 (2.0%) of returned monitors, monitor malfunction prevented complete data retrieval. In comparison, a trial in 380 asthmatics reported a 14.7% monitor failure rate with the MDILog and an additional 1.6% of missing monitors (Rand et al., 2007). In another recent study measuring adherence in 333 patients utilizing the Diskus Adherence Logger (DAL) and MDILog, 20% of monitors failed to download (Apter

et al., 2011). A prior paediatric study reported that 8% of Doser CT monitors failed with mechanical faults (O'Connor et al., 2004).

Smartinhaler malfunction during trial use was generally a consequence of a combination of patient and monitor-related factors. Problems such as fluid immersion, low battery, or electro-mechanical damage are likely to have been caused by both real-world use of MDIs by patients and the inherent vulnerability of electronic monitors to damage from environmental conditions. Many of these risks are difficult to reduce without affecting patient behaviour, which could then affect the generalisability of the data obtained. However, the within-trial checks allowed identification and subsequent removal of malfunctioning devices from further use and were a key factor in limiting data loss.

7.2.3 Dataset

The use of primary care clinic and hospital records ensured reliability in the collection of exacerbation and safety data. The integrity and completeness of the dataset for both electronic and clinic-recorded measurements minimised the effect of bias due to missing data.

7.2.4 Independent funding

The study was funded by the Health Research Council of New Zealand, a government funding organisation. AstraZeneca Limited (the manufacturer of Vannair and Symbicort) and Nexus6 Limited (the manufacturer of the electronic

monitors) had no involvement with the funding, concept, design, conduct or analysis of this study. The lack of non-commercially funded research has recently been identified as a possible limitation of the previous evidence base for the SMART regimen (Aalbers, 2013; DTB, 2011).

7.3 Generalisability of study findings

It is acknowledged that an open-label trial design allows the potential for bias. However, if a double-blind trial design had been used, patients randomised to the SMART regimen would have been required to use two inhalers, negating the potential advantages of single inhaler therapy and limiting the generalisability of the findings. High-risk patients from both primary care and hospital settings were recruited in this study and patients were not excluded on the basis of baseline beta-agonist overuse (Rabe et al., 2006a; O'Byrne et al., 2005) or lack of significant bronchodilator reversibility (Rabe et al., 2006a; O'Byrne et al., 2005). Furthermore, it was ensured that all patients were prescribed GINA Step 4 maintenance ICS and LABA therapy (GINA, 2011), thereby overcoming a criticism of previous studies (Cates and Lasserson, 2009), in which there was a reduction in maintenance ICS dose at randomisation (Rabe et al., 2006a; O'Byrne et al., 2005). These features ensure generalisability of the study findings to patients at risk of severe exacerbations in clinical practice (Rothwell, 2005).

MDIs rather than Dry Powder Inhalers (Turbohaler) were used to deliver budesonide/formoterol, as reliable, validated electronic monitors for the Turbohaler were not available. As the SMART regimen has only been approved for use with the budesonide/formoterol Turbohaler, the use of the budesonide/formoterol MDI in patients randomised to the SMART regimen can be considered 'off label'. Given that clinical comparability has been demonstrated for budesonide/formoterol via MDI and Turbohaler (Morice et al., 2008; Morice et al., 2007), it is proposed that the results are generalisable to the use of the budesonide/formoterol Turbohaler.

For the primary outcome variable, 56% and 45% of patients in the SMART and Standard groups respectively had at least one high beta-agonist use episode. Whilst this difference was not statistically significant, the lower margin of the confidence interval of the relative risk was close to one. However, this finding needs to be interpreted in the context of the unexpectedly common occurrence of budesonide/formoterol use above the four maintenance actuations by some patients on the Standard regimen. When this use was adjusted for in the sensitivity analysis, the proportion of Standard patients with at least one high use episode increased to 62%. Consequently, it is considered that these findings are consistent with the overall favourable risk/benefit profile of the SMART regimen demonstrated in this study.

7.4 Study Limitations

7.4.1 Equivalence ratio for budesonide/formoterol to salbutamol

For the definition of beta-agonist overuse, a 1:2 actuation ratio for budesonide/formoterol to salbutamol was used, based on recommended limits of beta-agonist use requiring medical review (National Asthma Council Australia, 2013; Holt et al., 2004) and supported by the short-term bronchodilator equivalence of 6µg formoterol to 200µg salbutamol with repeat dosing in acute asthma (Balanag et al., 2006; Rubinfeld et al., 2006). It is acknowledged that both higher and lower actuation ratios have been derived from single-dose studies in stable asthma (Hampel et al., 2008; Rosenborg et al., 2002).

7.4.2 Bioequivalence of oral prednisone to inhaled budesonide for the calculation of composite systemic corticosteroid exposure

For the calculation of composite systemic corticosteroid exposure, bioequivalent doses of 10mg oral prednisone to 5mg inhaled budesonide per day were used, determined in a prior dose-response study (Aaronson et al., 1998). This study (Aaronson et al., 1998) used adrenocorticotropic hormone (ACTH) infusion, which is a sensitive method for assessing the systemic effect of ICS on hypothalamic-pituitary-adrenal axis function (Barnes et al., 1998; Pedersen and O'Byrne, 1997). While the inherent limitations of such an estimate are acknowledged, this is the only study from which a validated measure of bioequivalence could be obtained.

7.4.3 Potential for dose dumping

Prior studies have reported that dose dumping has occurred in 12% to 32% of study participants who are electronically monitored (Rand et al., 1992; Mawhinney et al., 1991). In this current trial, dose dumping criteria were met in approximately 3% of the patients and on 0.5% of high use days when a previously used definition (Rand et al., 1992) was applied to the dataset. These findings indicate that the occurrence of dose dumping had limited impact on the dataset and justify the pre-specified plan to remove electronic medication use data on study visit days prior to analysis.

7.5 Future areas for further research

In the coming years, further research on the use of novel ICS/fast-onset LABA combination inhalers with the SMART regimen may provide clinicians with a greater range of inhaler devices which may be prescribed according to the SMART regimen.

The recommended treatment for patients with mild persistent asthma is regular ICS for maintenance therapy with SABA for relief. However, the potential benefits of regular ICS therapy may be limited by poor adherence to treatment. Prior studies have demonstrated that symptom-driven as-needed ICS with SABA therapy is an effective treatment in patients with mild asthma compared to regular ICS for maintenance with SABA for relief (Calhoun et al., 2012; Papi et al., 2007). Future research may study the use of symptom-driven as-needed ICS/fast-onset LABA therapy in patients with mild persistent asthma, as a novel approach which could

improve adherence to ICS treatment and asthma control compared with regular ICS therapy with SABA for relief.

7.6 Conclusion

This study has shown that combination budesonide/formoterol inhaler therapy prescribed according to the SMART regimen reduces severe exacerbations in 'real-world' at-risk asthma patients with high reliever medication use. This reduction in risk of severe exacerbations, compared with maintenance budesonide/formoterol and salbutamol reliever use, occurs without increasing the risk of beta-agonist overuse without medical review. Through electronic monitoring of actual medication use, it was possible to determine that the greater effectiveness with the SMART regimen was associated with both a reduction in non-adherence to maintenance budesonide/formoterol treatment, and the self-titrated escalation of budesonide/formoterol use in response to worsening asthma. Although patients prescribed the SMART regimen had a greater mean daily inhaled corticosteroid exposure, they had a lower oral corticosteroid exposure due to the reduction in severe exacerbations, resulting in a similar overall systemic corticosteroid burden.

Overall, the data suggest that the SMART regimen has a favourable risk/benefit profile and can be recommended for use by adult asthma patients at risk of severe exacerbations.

7.7 Acknowledgements

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This trial has been published: Patel, M., Pilcher, J., Pritchard, A., Perrin, K., Travers, J., Shaw, D., Holt, S., Harwood, M., Black, P. (deceased), Weatherall, M., & Beasley, R. 2013. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *The Lancet Respir Med*, 1, 32-42 [with permission to use from the publisher Elsevier].

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APPENDIX A: SMART STUDY PROTOCOL

Protocol

A randomised, controlled trial to investigate the "real-life" use of the Vannair® "SMART" regime in adult asthma (the SMART study)

Protocol No. SM01

Investigators

Professor Richard Beasley, Medical Research Institute of New Zealand

Dr Matire Harwood, Medical Research Institute of New Zealand

Associate Professor Mark Weatherall, University of Otago, Wellington

Dr Justin Travers, Medical Research Institute of New Zealand

Dr Kyle Perrin, Medical Research Institute of New Zealand

Dr Mitesh Patel, Medical Research Institute of New Zealand

Ms Amy Chan, University of Auckland

Mathew Williams, Medical Research Institute of New Zealand

Dr Shaun Holt, Clinicanz (for GP partners), Tauranga, New Zealand

Ms Ann Smith, Tu Kotahi Maori Asthma Trust, Wellington

Ms Cheryl Davies, Tu Kotahi Maori Asthma Trust, Wellington

Contact:

Professor Richard Beasley
Medical Research Institute of New Zealand
Level G, CSB Building, Wellington Hospital,
Riddiford Street, Newtown,
Private Bag 7902, Wellington 6242
New Zealand
Telephone: +64-4-805 0147
Facsimile: +64-4-389 5707
Email: richard.beasley@mrinz.ac.nz

Background

The recommended maintenance treatment for moderate and severe asthma in adults is regular inhaled corticosteroids (ICS) in combination with an inhaled long-acting beta-agonist drug (LABA) with a short-acting beta-agonist (SABA) used as rescue therapy. This therapy is commonly prescribed as a fixed combination inhaler, such as Seretide® (salmeterol xinafoate /fluticasone propionate) or Vannair® (budesonide/eformoterol metered dose inhaler) or Symbicort® (budesonide/eformoterol turbuhaler) and is taken twice daily ("STANDARD" regime). An alternative regime in which patients take their budesonide/eformoterol Single combination inhaler both as Maintenance And Reliever Therapy (referred to as SMART) has recently been proposed. A large clinical trial programme has shown that budesonide/eformoterol taken according to this regime is more effective than the STANDARD regime, and results in a reduction in severe exacerbations with improvements in symptoms and lung function being less consistent. However, these studies were undertaken under strict clinical trial conditions in highly selected populations and may have excluded poorly compliant and high-risk individuals who may benefit most from this regime in real life situations.

It is not clear how the use of budesonide/eformoterol given according to the SMART regime improves outcomes, or whether its use by patients in the situation of worsening asthma or severe exacerbations is associated with significant risk. To address these issues, it is necessary to assess the efficacy of budesonide/eformoterol given using the SMART regime in a population of high-risk asthmatics in real life. This would also provide the opportunity to assess the actual use of budesonide/eformoterol when used according to the SMART regime using electronic monitoring of inhaler use by patients.

Assessing the efficacy of the SMART regime in the NZ setting is of potential value in improving asthma outcomes for Māori. Māori are more likely to be hospitalised with asthma and yet less likely to be prescribed preventive medication, have an action plan or receive adequate education and improving asthma outcomes for Māori has been identified by the Ministry of Health as a health priority. Major barriers to Māori accessing satisfactory asthma care have been identified, including lack of a general practitioner, discontinuity of care, health being a low priority, lack of information and understanding, and lack of transport. These factors contribute to the historical higher rates of asthma mortality in Māori than other New Zealanders. The SMART regime has the potential to reduce many of these barriers and improve outcomes. If the SMART regime is shown to be highly effective and safe in high risk Māori with asthma, it can be widely recommended as the preferred approach. Conversely if the SMART regime is shown to have safety concerns with high use in severe exacerbations, awareness of this risk and caution in the use of the SMART regime in Māori with severe asthma can be advised. Hence, Māori participation in the study is important and the researchers will endeavour to make the study accessible to Māori and will involve local Maori Health providers in the recruitment process.

Hypothesis

Our primary hypothesis is that there are variable patterns of use of a single combination inhaler (Vannair - budesonide/eformoterol) when taken as part of the SMART regime compared with when used with Ventolin as a reliever and that some of these patterns may potentially lead to risk in 'real-life' asthmatic patients in the setting of an exacerbation.

Objectives

1. To determine whether budesonide/eformoterol as taken via the SMART regime will lead to reduced use of PRN/rescue inhalations of medication as compared to STANDARD therapy in real life asthmatics with a recent severe exacerbation.

2. To determine the actual use of budesonide/eformoterol according to the SMART regime including patterns of use in the situation of worsening asthma and severe exacerbations.

3. To determine the actual use of budesonide/eformoterol when used as part of a STANDARD management plan with Ventolin as a reliever, including patterns of use in the situation of worsening asthma and severe exacerbations.

4. To determine whether budesonide/eformoterol given as per the SMART regime reduces the number of asthma exacerbations when compared to STANDARD therapy in high-risk asthmatics in real life.

5. To determine whether budesonide/eformoterol given as per the SMART regime leads to better control of asthma than STANDARD therapy in high-risk asthmatics in real life.

6. To determine the satisfaction that patients have with their inhaled asthma treatment regime.

7. To determine whether patterns of bronchodilator use can predict the onset of severe exacerbations.

Outcome variables

Primary:

- The proportion of high beta-agonist use episodes in the SMART group compared with the Standard group. This is defined as the proportion of patients in the SMART group who at any point within the 6 month study period used greater than 8 actuations of Vannair **as a reliever** (i.e. greater than a total of 12 puffs) per 24 hour period compared to the proportion of patients in the Standard group who used greater than 16 actuations of Ventolin in a 24 hour period.

Secondary:

Measure of high use of 'as required' medication

- Number of days within the 6 month study period that greater than 8 actuations of Vannair as a reliever were taken by patients in the SMART group (within a 24 hour period) compared with greater than 16 actuations of Ventolin for the Standard group.

- The frequency of high use episodes per patient in the SMART group compared with the Standard group (high use being defined as greater than 8 actuations of Vannair as a reliever in the SMART group and greater than 16 actuations of Ventolin in the Standard group, per 24 hour period).

Measure of marked overuse of 'as required' medication

- The proportion of patients in the SMART group who at any point within the 6 month study period used greater than 12 actuations of Vannair as a reliever (i.e. greater than a total of 16 puffs) per 24 hour period compared to the proportion of patients in the Standard group who used greater than 24 actuations of Ventolin in a 24 hour period.

- Number of days within the 6 month study period that greater than 12 actuations of Vannair as a reliever were taken by patients in the SMART group (within a 24 hour period) compared with greater than 24 actuations of Ventolin for the Standard group.

- The frequency of overuse episodes per patient in the SMART group compared with the Standard group (overuse being defined as greater than 12 actuations of Vannair as a reliever in the SMART group and greater than 24 actuations of Ventolin in the Standard group, per 24 hour period).

- The proportion of patients in the SMART group who at any point within the 6 month study period used greater than 16 actuations of Vannair as a reliever (i.e. greater than a total of 20 puffs) per 24 hour period compared to the proportion of patients in the Standard group who used greater than 32 actuations of Ventolin in a 24 hour period.

- Number of days within the 6 month study period that greater than 16 actuations of Vannair as a reliever were taken by patients in the SMART group (within a 24 hour period) compared with greater than 32 actuations of Ventolin for the Standard group.

- The frequency of overuse episodes per patient in the SMART group compared with the Standard group (overuse being defined as greater than 16 actuations of Vannair as a reliever in the SMART group and greater than 32 actuations of Ventolin in the Standard group, per 24 hour period).

- Proportion of patients in the SMART group who use greater than 8 actuations of Vannair as a reliever (within a 24 hour period) without subsequent review by a healthcare professional (as specified in the self management plan) compared with the proportion of patients in the Standard group who use greater than 16 actuations of Ventolin without subsequent review by a healthcare professional.

- Number of days and frequency of episodes per patient that greater than 8 actuations of Vannair as a reliever are taken by patients in the SMART group (within a 24 hour period) without subsequent review by a healthcare professional (as specified in the self management plan) compared with the number of days that greater than 16 actuations of Ventolin are taken by patients in the Standard group without subsequent review by a healthcare professional.

- Maximum number of reliever inhalations (n-4 Vannair for SMART group and n=Ventolin for Standard group) per 24 hour period in each of 4 week periods.

- Maximum number of reliever inhalations (n-4 Vannair for SMART group and n=Ventolin for Standard group) per 24 hour period as a mean of the individual patient maximums, for the total study period.

- Maximum number of inhalations (Vannair® for SMART group and Vannair and Ventolin combined for Standard group) per 24 hour period in each of the last 3 study periods (weeks 3-10, 10-17, 17-24 respectively) and for the total study period.

Measure of underutilisation of regular medication

- The proportion of patients who underuse their maintenance Vannair treatment at any point within the 6 month study in the SMART versus standard groups (0 or 1 inhalations within a 24 hour period).

- The number of patient days when maintenance Vannair treatment was underused during the 6 month study period in the SMART versus Standard groups (0 or 1 inhalations within a 24 hour period).

- The frequency of underuse episodes per patient in the SMART group compared with the Standard group (underuse being defined as 0 or 1 inhalations within a 24 hour period.

Efficacy

- Asthma Control Questionnaire (ACQ) Score at each study visit in SMART versus standard.
- Time to first high beta agonist use episode and/or severe exacerbation.
- Number of severe exacerbations (see definition of severe exacerbation below).
- Number of hospital admissions.
- Forced Expiratory Volume in 1 second (FEV1) at each study visit.

Steroid Load

- Mean daily inhaled corticosteroid (ICS) dose in SMART versus standard groups.
- The proportion of patients in the SMART versus standard groups who required treatment with systemic corticosteroids.
- Number of treatment days with systemic steroids in SMART versus standard groups.
- Mean number of courses of systemic steroids in SMART versus standard groups.
- Composite steroid load combining ICS and systemic steroid treatment.

Patterns of use of medication

- The number of actuations of reliever Vannair (n-4) and Ventolin per day in the 14 days pre and post severe exacerbation, with D0 being the day of first treatment with systemic steroid or high beta agonist use episode (D-14 to D+14).
- Number of actuations of reliever Vannair (SMART) and Ventolin (Standard) on days -5 to 0 as predictors of risk of future exacerbation (ROC curves).

Qualitative

- Satisfaction with Inhaled Asthma Treatment Questionnaire (SATQ) pre- and post-study participation and between groups at the end of the study.

Management Plans

- For Standard group, compare ACQ, FEV1, severe exacerbation rate, hospital admissions, ED/urgent visits in the 6 months pre study (data at visit 1 to be a marker of this) versus the 6-month study period.

- For the Standard group, describe the pattern of use of Ventolin and Vannair.

Maori patients

Compare differences in all the above outcomes in the subgroup of Maori patients for SMART and standard.

DEFINITIONS

For the purposes of this study, a high beta agonist use episode is defined as greater than 12 inhalations of Vannair total in any 24 hour period for the SMART group and greater than 16 inhalations of Ventolin in any 24 hour period for the Standard group.

As per the SMART self management plan, this definition accounts for a worsening in asthma symptoms together with an increase in reliever Vannair use and a recommendation to seek medical assessment on that day. This would in effect include any patient who uses more than 8 reliever puffs of Vannair in any 24 hour period (i.e. assuming a maintenance use of Vannair of 4 puffs a day as per the management plan).

As per the Standard self management plan, this definition accounts for a worsening in asthma symptoms together with an increase in Ventolin use to 1-2 puffs every 2-3 hours and a recommendation to seek medical assessment within the next 1-2 days. This would in effect include any patient who is using more than 2 puffs of Ventolin every 3 hours (16 inhalations per 24 hours).

A severe exacerbation is defined as either: a) the use of systemic corticosteroids (tablets, suspension or injection), or an increase from a stable maintenance dose (for patients commenced on prednisone after commencement of the study), for at least 3 days; or b) a hospitalization or ER visit because of asthma, requiring systemic corticosteroids) [1].

A composite measure of severe exacerbation will use a combination of high beta agonist use and/or prednisone use.

A 24-hour period is defined as 0300-0259.

Study Design

This will be an open-label, randomised, controlled trial undertaken in 3 centres in New Zealand. Subjects will be randomised (in a ratio of 1:1) to receive budesonide/eformoterol (given as a Vannair® MDI) according to one of the two following treatment regimes:

1. budesonide/eformoterol twice a day and as needed (SMART).

2. budesonide/eformoterol twice a day along with a salbutamol (Ventolin®) metered dose inhaler (MDI) as required (STANDARD Treatment).

Subjects

Three hundred individuals who have a severe exacerbation of their asthma in the previous 12 months will be recruited from Wellington, Tauranga and Auckland. Potential sources of recruits include the Hospital Emergency Departments, Accident and Medical Clinics, Māori Health Providers, General Practitioners, and subjects in research volunteer databases. It is intended that the total recruitment target of 300 subjects will be divided between the Wellington, Auckland and Tauranga centres and that at least 20% of the study participants will be Māori. This strategy will be revisited if recruitment success at the three centres varies greatly.

Inclusion criteria:

- Doctor diagnosis of asthma
- 16 to 65 years old
- Current prescription for ICS
- No change in the dose of ICS in the last month.
- An exacerbation in the previous year where the patient presented to a GP or an Emergency Department and was prescribed a course of oral steroids and/or received a spacer-delivered or nebulised bronchodilator and patients who self-administered prednisone for asthma for at least 3 days.

Exclusion criteria:

- Onset of respiratory symptoms after the age of 40 years in current or ex-smokers with a ≥10 pack years smoking history
- Use of an at-home nebuliser [unless patients agree to withhold nebuliser use for the study duration]
- Treatment with oral prednisone in the previous four weeks

- Diagnosis of COPD, interstitial lung disease or bronchiectasis.
- Diagnosis of congestive heart failure
- Unstable coronary artery disease or unstable angina
- Atrial fibrillation or other cardiac arrhythmias.
- Uncontrolled depression or anxiety disorder.
- Malignancy with life expectancy of less than one year.
- Unwilling or unable to switch from current asthma treatment regime or management plan. Subjects on other long-acting beta-agonists (LABAs) at the time of study screening will be switched directly to Vannair®. No washout period is required.
- Any other safety concern at the investigator's discretion.
- Inability to understand the study requirements and/or unwillingness to give consent to participate in the study.

Study Procedures

Study visits will primarily be conducted at the study centres for the Wellington, Auckland and Tauranga sites or arrangements may be made to conduct study visits at the subject's home or workplace for the Tu Kotahi and Auckland sites.

Initial Telephone Screening

Patients who are potentially suitable to participate in the study will be asked initial screening questions relating to the inclusion/exclusion criteria, to determine their eligibility for the study. Patients identified as being eligible will be sent the Participant Information Sheet and a date/time arranged for Visit 1. Patients are able to continue to take their regular inhaled therapy prior to all study visits, without needing to withhold their medication prior to spirometry. Patients will be asked to bring all current inhalers with them to their first study visit, in order to replace them with study medication.

Visit 1 (Week 0)

At first study visit, written consent will be obtained prior to any study-specific procedures. The subject's demographics and medical and medication history will be taken, and the subject's eligibility for the trial confirmed according to the inclusion and exclusion criteria. Spirometry (FEV1 and FVC) will be performed. Spirometry will be measured according to a standardized protocol (See MRINZ SOP 'Spirometry for SMART study'). The investigator will complete the ACQ with the patient. The SATQ will also be completed and the questionnaire retained by the Investigator for later analysis. The subject will be randomised and study medication dispensed. All current inhalers will be collected from patients.

For the Standard group, 1 Vannair and 1 Ventolin inhaler will be issued, with 1 further Vannair and Ventolin each to be provided in a sealed envelope in case of emergency use. For the SMART group, 3 Vannair inhalers will be provided (one of which will be sealed in an envelope for emergency use). Each Vannair and Ventolin inhaler contains 120 doses. Inhaler technique will be checked as will peak flow technique (if appropriate). Advice on care of the inhaler device will be provided in written format for the patient. Self management plans will be issued to patients according to their randomization status and prior peak flow monitoring use.

The next study visit date will be booked for a date approximately 3 weeks later, with a written reminder being provided. At the patient's preference, a text message via mobile telephone or a telephone call will be made 2-3 days prior to the next study visit in order to confirm suitability of the date and time.

Patients will be requested to make on note on their appointment card of the starting date and duration for any courses of steroids that they take in the following weeks.

Visits 2, 3, and 4 (weeks 3, 10, and 17)

At visits 2-4, the study participants will complete the ACQ and spirometry, and they will be asked about any changes in health (including asthma exacerbations, ED visits or hospital admissions) or medication since their first visit. The Vannair and Ventolin inhalers previously issued will be collected from the participants and replacement inhalers issued. On collection of the used inhalers from the patients, their correct function will be validated according to a standard protocol (see MRINZ SOP 'Inhaler device Validation').

For the Standard group, 2 Vannair and 2 Ventolin inhalers will be issued at each visit. For the SMART group, 3 Vannair inhalers will be issued at each visit. The next study visit date will be booked for a date approximately 7 weeks later, with a written reminder being provided. A text message or telephone call 2-3 days prior to the appointment will be made to confirm the date and time.

Should there have been any change in the subject's health or medication use considered to be exclusionary by the investigator the subject will be excluded from further study.

Visit 5 (week 24)

At visit 5 the study participants will complete the ACQ, SATQ, and spirometry, and the subjects will be questioned about any changes in health (including asthma exacerbations) or medication since their first visit. The Vannair and Ventolin inhalers previously issued will be collected from the participants. The participants will be prescribed their pre-study inhaled asthma medication and advised to discuss any potential changes of therapy for the future with their GP. A letter will be sent to their GP advising them of this.

Asthma Control Assessments

The Asthma Control Questionnaire (ACQ), English Version for New Zealand (November 2001), will be completed by the Investigator with the participants at all study visits, and the ACQ score calculated.

At each study visit after randomisation, subjects will also be asked if they have experienced an exacerbation of their asthma since the last visit including details of unscheduled visits to their General Practitioner or Accident and Medical Clinic/Emergency Department and courses of prednisone. This information will be validated by cross-checking as appropriate with the relevant health service provider.

Satisfaction with Inhaled Asthma Treatment Questionnaire (SATQ)

The Satisfaction with Inhaled Asthma Treatment Questionnaire (SATQ) (*Campbell et al* 2003) will be completed at study visits 1 and 5 by all participants.

Spirometry

FEV1 and FVC will be measured at every study appointment. Study participants will not be required to with-hold from using their inhalers prior to the study appointments and spirometry testing; however, reasonable efforts should be made to conduct each subject's study appointments at approximately the same time of day each time. Spirometry will be performed according to a standardized protocol.

Reversibility testing will not be performed at the first study visit as this data is unlikely to provide us with any additional information about the study participants. Measures of baseline asthma control will be obtained from exacerbation history, prior steroid use and ACQ. Additionally, this will mean that study participants will not be required to hold their inhaled treatment prior to any study visits.

Compliance assessments/Inhaler downloads

A Nexus6 recording device will be incorporated in the each of the inhaler sleeves issued to study subjects, and will record each inhalation that occurs. An electronic record of the date and time of all actuations occurring since the last study visit will be downloaded after study appointments 2-5 (see details above). A participant information sheet will be provided on the care of the device and contact numbers in case of inhaler damage. Though patients will be provided with sufficient inhalers to account for the 4 study periods, should the patient require replacement inhalers in the intervening time, they will be asked to contact their investigator. Patients will be advised to contact the local Investigator if they open their 'emergency envelope' inhaler. The investigator can then co-ordinate replacing any used medication canisters as required.

Inhaler use data on the day of the study visit will be discounted for the purposes of statistical analyses, in order to avoid erroneous data triggered by an upcoming study visit/dose dumping and to discount the validation actuations performed by the investigator from being included in the analysis.

Inhaler devices will have individual ID numbers attached and will remain patient-specific during the course of the study.

Any devices damaged or malfunctioning during the course of the study will be returned to MRINZ and/or Nexus6 for testing.

Management Plans and Peak Flow Monitoring

At the first study visit study subjects randomised to STANDARD treatment will be provided with an "Asthma Self Management Plan" leaflet based on The Asthma and Respiratory Foundation of New Zealand (Inc.) for their reference. Subjects randomised to the SMART regime will instead receive a management plan based on the "My Symbicort® SMART Asthma Action Plan" sheet issued by Astra Zeneca, the manufacturers of Vannair® and Symbicort®. The purpose of issuing these advisory documents is to replicate the advice and support a patient would normally receive when attending a medical consultation for their asthma.

Subjects will not be required to monitor their peak flows in order to participate in the study; however, those subjects who are already doing so will be supported to continue to do so by issuing them with a management plan appropriate to their randomisation status that relates to their peak flow.

In summary:

Patients randomized to SMART group:

Patients who do not monitor their peak flows will receive the 'My Asthma Action Plan - Symptoms'.

Patients who monitor their peak flows will receive the 'My Asthma Action Plan – Peak Flow'.

Patients randomized to Standard group:

Patients who do not monitor their peak flows will receive the Asthma and Respiratory Foundation of NZ 'Asthma Self management plan', modified with no peak flow monitoring.

Patients who monitor their peak flows will receive the Asthma and Respiratory Foundation of NZ 'Asthma Self management plan' incorporating peak flow readings.

For the purpose of this study, a drop in Peak flow to 60% of recent best will signify a deterioration in asthma control recommending contact with a doctor and consideration of treatment with a course of oral steroids. Prednisone courses of 40 mg per day for 5 days will be recommended for both SMART and Standard patients.

A drop in peak flow to 40% of recent best will signify an asthma emergency, recommending urgent medical review.

Inhaler technique will be discussed and checked at visit 1. Those patients who are found to have sub-optimal technique will be offered a spacer device, in line with current clinical practice. A record of this will be kept.

Inhaler technique and management plans will be reviewed with the patient at Study Visit 3.

Study visit windows and failure to attend study appointments

Study visits are to be scheduled to occur within +/- 3 days of their due date; however if this is not possible for some reason or they have to be held early or postponed the visit window may be extended up to +/- 7 days. Subjects may also arrange to attend their appointments earlier than this if their medications are running low. If a subject fails to attend their study appointments at the study clinics they will be contacted by telephone and arrangements made to visit them at home or work to conduct the study visits. Permission to conduct this follow-up will be obtained as part of the informed consent process.

Schedule of assessments

Visit Number	1	2	3	4	5
Week	0	3	10	17	24
Informed consent*	X				
Demographics and medical history	X				
Medication history	X				
Eligibility criteria assessment	X				
Spirometry (FEV1 & FVC)	X	X	X	X	X
ACQ	X	X	X	X	X
SATQ	X				X
Randomisation	X				
Issue management plan	X				
Check peak flow and inhaler technique	X		X		
Inform GP of inclusion in study	X				
Provide written appointment reminder card with integrated steroid recording	X	X	X	X	
Text/telephone reminder of study visit	X	X	X	X	X
Adverse events and concomitant medications review		X	X	X	X
Asthma exacerbations review		X	X	X	X
Dispense medication	X	X	X	X	
Return patient to pre-study medication					X
Compliance assessments / Inhaler download		X	X	X	X
Validation of device according to SOP		X	X	X	X
Trial completion					X
Inform GP of completion of study					X

* Informed consent form must be signed before any trial-related procedure takes place

Study Treatments

Following enrolment, patients will be randomised to treatment with either:

- Vannair® 200/6µg taken as 2 inhalations twice a day and as required as a reliever (SMART treatment regime).

OR

- Vannair® 200/6µg taken as 2 inhalations twice a day and Ventolin® 100µg as required (STANDARD treatment regime).

Dose determination

All patients entering the study will be prescribed Vannair 200/6 µg 2 inhalations twice a day as their maintenance therapy, irrespective of their prior inhaled corticosteroid (ICS) dose. As patients with recent asthma exacerbations are being recruited into the study, in order to optimize their asthma therapy and improve patient safety, patients with prior 'low dose' inhaled corticosteroid therapy (fluticasone propionate $\leq$ 125 µg twice daily or budesonide/beclomethasone dipropionate $\leq$ 200 µg twice daily) will be stepped up to a higher ICS dose at study entry.

Randomization

This will occur by sealed envelope provided to study sites, with a block size of 8 for the randomisation schedule.

Spacer use

Subjects who have problems with the use of an MDI will be provided with a spacer and will be encouraged to use it. Other participants will be provided with a spacer if they request one.

Inhaler downloads

The participants are to be told that they are using a modified inhaler that has been produced specifically for this study to count the number of doses used since the last study visit and that the purpose of the study is to compare the benefits of the two Vannair regimes and to determine whether the amount used influences outcome. Participants should be reminded to avoid using other inhalers as this will affect the accuracy of the study data, and it should be explained that the study inhalers need to be "down-loaded" at each visit.

Subjects will not be told that the date and time of each dose will be recorded as this may influence their usage. A review of the date and time of each inhaler actuation should be conducted to determine if a subject "dose-dumps" and if dose-dumping is suspected it will be documented and reported. Electronic data collected relating to inhaler actuations on the day of each study visit will be excluded from the study analysis in order to minimise the possibility of including dose-dumping data and erroneous data originating from the device validation actuations.

Safety Monitoring

Adverse Events

An adverse event is any untoward medical occurrence in a study subject temporally associated with participation in the trial and the administration of study medication, whether or not considered related to the medicine. An adverse event can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of the study treatment. A worsening of a pre-existing medical condition other than asthma will be considered an adverse event - please see the section entitled "Asthma Exacerbations" for details on the handling of asthma exacerbations.

Adverse event data will be collected and analysed with efficacy data at the end of the study. Serious adverse events will be notified to the multi region ethics committee within 24 hours of the investigators becoming aware of them.

- **Serious Adverse Events (SAEs)**

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

- Death
- Life-threatening event
- Permanently disabling or incapacitating event
- Hospitalisation or prolongation of hospitalisation. Hospitalisation for the purposes of SAE reporting is defined as an admission to hospital and does not include a presentation to the Emergency Department followed by discharge without admission or an admission for elective reasons
- Any event considered serious by the study investigator

Should a female subject on the trial become pregnant during the course of the trial, the pregnancy itself will not be regarded as an SAE although it will be reported to the Ethics Committee in an expedited manner. Current clinical practice allows for the use of combination budesonide/eformoterol during pregnancy, as the benefits to both mother and child of adequate asthma control outweigh the theoretical risks of treatment. Thus, the risks and benefits of continuing or withdrawing from the study will be discussed with pregnant patients on an individual basis. In any event, the subject will be asked to contact the researchers after the birth of the baby and any congenital anomaly or birth defect will be considered to be an SAE.

Asthma Exacerbations

If a study participant has an exacerbation during the study or they have a worsening of their asthma control, they will be asked to contact their General Practitioner for assessment and management or visit an Accident and Emergency Department/Clinic in their area. It will be reinforced to the study participants that they will receive standard medical care (from their GP, after hours or ED) for their asthma during the course of the study.

- Study subjects randomised to the SMART regime will be advised that should they take more than 12 doses in total of Vannair over any 24 hour period or more than 6 doses on a single occasion they should see their doctor or attend the Accident and Emergency Department/Clinic in their area.

- Study subjects who are randomised to the STANDARD regime will be given instructions to see their doctor or attend the Accident and Emergency Department/Clinic in their area if they require their salbutamol more than every 2-3 hours.

As per the SMART and Standard asthma self management plans, patients will be asked to start a course of prednisone and seek medical review as they notice that their asthma control is deteriorating. Patients who have previously kept a course of prednisone at home for emergency use will be supported in continuing with this aspect of their self-management plan and they will be advised to seek replacement courses of steroids from their primary health provider. It will be explained to these patients that whenever a course of prednisone is commenced by them, they must seek medical review as per their self management plans.

Patients who do not have courses of steroids at home for use in an emergency will be advised to seek medical review as per their management plans.

Study participants will be advised to discuss all General Practitioner or Accident and Emergency Department/Clinic visits, together with hospital admissions, for troublesome asthma with their study contact at their next study visit. Participants will also be asked to keep a record of the date of commencement and duration of treatment (in days) of steroids used for treatment of their asthma, on their appointment reminder card. This data can then be used to help determine patterns of use of medication around the time of worsening asthma control/exacerbation.

As assessing the comparative efficacy of the medication regimes in asthma control is an objective of this study, asthma exacerbations that do not meet the criteria for being considered an SAE will not be reported as adverse events but the data concerning these events will be collected as measures of study outcomes.

Local Co-ordinating Investigators (LCIs)

Drs Harwood (Auckland), Holt (Tauranga) and Patel (Wellington) will have the role of local co-ordinating investigators (LCI) for each of the 3 sites.

The LCI's role will be to act as a point of local contact for any day-to-day issues related to the Study, with Dr Patel in Wellington being the Principal Investigator.

Independent Safety Monitoring

An interim safety statistical analysis will be conducted by the study statistician Associate Professor Mark Weatherall for all unplanned hospitalisations for asthma. This analysis will be performed masked to treatment allocation (the results for analysis will be provided without the patient ID code, but with the blinded randomised treatment code (e.g. treatment 1 or treatment 2). The results of this analysis will then be reviewed by an independent safety monitor. Dr Andrew Brant, Consultant Respiratory Physician & Clinical Director of Medicine, North Shore Hospital, who is independent from the study team, will act in this capacity.

The calculated interim P value for performing a safety review of the study (using the ld98 Program), assuming one interim analysis halfway through the data collection, is 0.006 (using a one sided O'Brien-Fleming bound).

The proportion of participants who have had an unplanned hospitalisation for asthma will be compared to the expected proportion of 4.5% using the binomial test for proportions. If the observed rate exceeds the expected rate with a P value less than 0.006, a safety review of the study will be undertaken. The P value calculations use the ld98 program, an alpha spending function, with alpha nominated as 0.05, evenly distributed analysis times, and O'Brien Fleming boundaries. The expected proportion is derived from data from the Wairarapa Māori asthma project in the book Te Reo o te Ora 2nd ed.1999 ISBN 1-877243-18-0.

If the findings of the safety analysis indicate a safety review is necessary then termination of the trial will be considered.

Power and Statistical Methods

Sample Size and Study Power

The actual use of beta agonist in the context of an asthma exacerbation has not been defined and prior studies have shown variable rates of asthma exacerbations in patients.

In the RELIEF study, 43% of the patients with Stage 4 asthma severity had at least one exacerbation over a 6 month period[2]. A pooled analysis of studies in moderate-severe asthmatics showed an exacerbation rate of 1.5 per year in the control group[3]. One of the primary SMART studies reported that 22% of patients with a recent severe exacerbation and who were receiving maintenance budesonide/eformoterol and as needed terbutaline experienced a severe exacerbation over a 12-month period[4]. Thus, for the purposes of this study, we would predict that about 40% of asthmatics might have a severe exacerbation (defined as requiring systemic corticosteroids) over a 6 month period.

A prior NZ study showed that 85% of patients admitted to hospital with asthma exacerbations reported using $\geq$ 16 actuations of short acting beta agonist in the 24 hours prior to admission[5]. There is, however, uncertainty as to the actual use of beta agonist in the context of a severe asthma exacerbation not requiring hospital admission. Also, it is not certain what proportion of patients use greater than 16 inhalations and are not prescribed oral steroid therapy, and thus not meet the severe exacerbation definition used above.

If we assume half of patients will have an episode of 'high beta agonist use' (greater than 16 actuations of Ventolin or equivalent) in the setting of a severe exacerbation (20% of total) and an additional 20% of the remaining 80% of patients have an episode of high beta agonist use, then about 36 % of asthmatics will be expected to have a high beta agonist use episode over 6 months in the Standard group.

If 300 individuals are recruited, it is predicted that around 108 patients will have a high use episode over the course of the study. 150 patients in each treatment arm will have an 80% power ($\alpha = 0.05$) to detect an exacerbation rate of 21.4%, an absolute reduction of around 15%, a relative risk of just under 0.6.

A secondary outcome is the ACQ score. Previous studies suggest that the participants are likely to have an ACQ score of 2.0 ± 1.0 (SD) at baseline. If α=0.05 we will have 80% power to detect a difference between the treatments in the ACQ score of 0.32 if we have 150 participants in each group. Only 128 participants in each group would be required to detect a difference of 0.50 in the ACQ score.

The study is aiming to recruit a minimum of 60 Māori subjects (at least 20% of the total study recruitment). The study will not be powered to provide statistically significant findings concerning the differences in treatment regimens on beta agonist high use episodes or asthma control for Māori but will provide valuable information about patterns of use of this medication in Māori including information about whether Māori patients use their inhalers differently to non- Māori patients.

The primary analysis will be a binomial test of difference in proportions, expressed as a relative risk, for the proportions in the two groups with a beta agonist high use episode. t-tests will be used to compare mean ACQ scores and other continuous variables by randomised group. Should normality assumptions not be met for this analyses then data transformations will be sought that might lead to normality assumptions being met or failing this a non-parametric technique, the Mann-Whitney test will be used. The secondary outcome variables: ACQ, FEV1, FVC, inhaler actuations per day (during an exacerbation or averaged over 4 week periods), will also be analysed using mixed linear models to account for repeated measurements and examine patterns of change with time.

References

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2. Pauwels RA, Sears MR, Campbell M, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. Eur Respir J 2003; 22: 787-94.

3. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy 2005; 60: 302-308.

4. Rabe KF, Atienza T, Magyar P, et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006; 368: 744-753.

5. Windom HH, Burgess CD, Crane J, et al. The self-administration of inhaled beta agonist drugs during severe asthma. NZ Med J 1990; 103:205-7.

File notes (added 7 June 2012)

1. Page 5, Primary Outcome variable. For grammatical correctness, the first sentence should read 'The proportion of *patients with a* high beta-agonist use episode in the SMART group compared with the Standard group'. The next sentence clearly defines the primary outcome variable.

2. Page 11, line 4. Erratum: each Vannair inhaler contains 120 doses and each Ventolin inhaler contains 200 doses.

3. Page 20, Sample Size, 2nd sentence in paragraph 2. There is a typographical error: the sentence should read: '150 patients in each treatment arm will have an 80% power (α = 0.05) to detect ~~an exacerbation~~ *a high use episode* of 21.4%, an absolute reduction of around 15%, a relative risk of just under 0.6'. The preceding 2 paragraphs detail the approach used to calculate the power based on an episode of high beta agonist use, in line with the primary outcome variable and hypothesis.

APPENDIX B: PARTICIPANT INFORMATION SHEET AND CONSENT FORM

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

Postal address:
Private Bag 7902, Wellington 6242
New Zealand
Telephone: +64 4 805 0147
Facsimile: +64 4 389 5707
Physical address:
Level 7, CSB Building
Wellington Hospital
Riddiford Street, Wellington 6021
New Zealand
Website: www.mrinz.ac.nz

DIRECTOR
Professor Richard Beasley
MBChB, FRACP, DM(Southampton), FAAAAI, FRCP(London), DSc(Otago)
Visiting Professor
University of Southampton, UK
richard.beasley@mrinz.ac.nz

MANAGER
Denise Fabian
denise.fabian@mrinz.ac.nz

PROGRAMME DIRECTORS

ALCOHOL & DRUG ABUSE
Geoffrey M Robinson
MBChB, FRACP, FAChAM

ASTHMA
Richard Beasley
MBChB, FRACP, DM(Southampton), FAAAAI, FRCP(London), DSc(Otago)

COMPLEMENTARY MEDICINE
Shaun Holt
BPharm, MBChB

COPD
Justin Travers
MBChB, FRACP

INFLUENZA
Kyle Perrin
MBChB, FRACP

MAORI & PACIFIC HEALTH
Matire L N Harwood
MBChB

PATIENT SAFETY
Philippa M Shirtcliffe
MBChB, FRACP

PHARMACOVIGILANCE
Kyle Perrin
MBChB, FRACP

STROKE
Harry K McNaughton
MBChB, FRACP, FAFTM, PhD

VENOUS THROMBOEMBOLISM
Richard Beasley
MBChB, FRACP, DM(Southampton), FAAAAI, FRCP(London), DSc(Otago)

Participant Information Sheet

Short Study title:

A study to investigate the "real-life" use of the Vannair® "SMART" regime in patients with asthma (the SMART study)

Introduction

You are invited to take part in a clinical research study. Please take as much time as you need to read this information sheet carefully to determine if the study is of interest to you. You may wish to discuss the information in this sheet with your family or whanau. Please ask us if you have any questions about the study. Your involvement in this study is voluntary and you have the right not to take part and to withdraw at any time.

What is the aim of the study and what is being tested?

One of the types of medicines commonly used to treat asthma is called "inhaled corticosteroids". Examples of inhaled steroids include Pulmicort® and Flixotide®. Another type of medicine that is also used to treat asthma is "long acting inhaled beta-agonists". Examples of this type of medicine include Oxis® and Serevent®. The two different types of medicines are often combined in a single inhaler. Examples include Seretide®, Vannair® or Symbicort®. These combination inhalers are usually taken twice daily as maintenance therapy while another inhaler (often Ventolin®) is used as a "Reliever" medication if your asthma worsens. In the rest of this information sheet we will refer to this as a "Standard" regime. An alternative way of treating patients with moderate and severe asthma is for the combination inhaler to be used not only twice a day as a maintenance therapy but also as a reliever therapy with extra puffs taken when your symptoms are worse. This alternative method is referred to as the "SMART" regime which stands for "Single combination inhaler as Maintenance And Reliever Therapy" and it has recently been proposed by the makers of Vannair® and Symbicort®.

Previous research has shown that Symbicort® taken according to the SMART regime is associated with fewer asthma attacks compared with the Standard regime. However, it is not clear why this is or if this would be the case in "real-life" when people are not being closely monitored as they were in the previous research studies. Vannair® and Symbicort® contain exactly the same medicines in the same doses. Vannair® is a metered dose (aerosol) inhaler while Symbicort® is a turbuhaler (dry powder) inhaler. The safety and effectiveness of these inhalers are comparable. Both Symbicort® and Vannair® have been approved as prescription medications in New Zealand and are currently in use by asthmatic patients. Symbicort®, but not Vannair®, is currently approved for use according to the SMART regime. In this study, we are using the aerosol inhaler Vannair® rather than the powder inhaler Symbicort®.

This study aims to compare the effectiveness of Vannair® taken following the SMART regime compared with the Standard regime in people with asthma. We want to try and make the study experience as close to "real-life" as possible so unlike other asthma studies we will not require you to complete any diary cards between study appointments. We will however use a small electronic device attached to your inhaler to measure the total number of puffs that have been used from each inhaler because this provides information about how well controlled your asthma is.

How many people are taking part and where will the study be conducted?

We are planning to recruit 300 people from Auckland, Tauranga and Wellington (approximately 50 people from Auckland, 100 people from Tauranga and 150 people from Wellington). In Wellington the study is being conducted by the Medical Research Institute of New Zealand in association with the Tu Kotahi Maori Asthma Trust. In Auckland, the study is being conducted by the MRINZ in association with Te Hononga O Tamaki Me Hoturoa Healthcare and Clinicanz in association with partner GP practices; in Tauranga, the study is being conducted by Clinicanz in association with partner GP practices.

If you live in the Wellington area and take part in the study, you can choose which location will be most convenient for you to attend your study visits. We will be running the study at Wellington Hospital in Newtown, Bowen Hospital in Crofton Downs, Hutt Hospital in Lower Hutt and at the Tu Kotahi Maori Asthma Trust at Kokiri Marae in Seaview, Lower Hutt. Our team from the Tu Kotahi Maori asthma trust can also arrange to visit you at your home or workplace.

What will the study involve?

One of the study co-ordinators or doctors will talk to you about the study and you will be given a copy of this information sheet to read and discuss with your family or whanau. If you are willing to participate in the study you will be asked to sign an Informed Consent form. This form shows that you have been given all the information about the study and that you understand what is involved. You will be asked to sign this form before any of the study tests take place. If you have any questions at any stage please ask the study co-ordinator or doctor.

This study requires 5 visits over a period of approximately 24 weeks. The first visit will take about 45 minutes and the later visits will take about 30 minutes.

What happens at the first study visit?

If you choose to participate, at the first visit you will be asked some questions about your general health, your asthma and any medications you are using. Tests of your breathing by spirometry will be done to see how your lungs are working and you will complete 2 questionnaires about your asthma. These checks are done to ensure it is suitable for you to participate in the study.

Once it is confirmed that you are able to participate you will be randomly assigned to receive treatment according to either the:

- SMART regime (Vannair® 200/6 µg, 2 puffs twice a day plus extra doses as a reliever)

  Or

- Standard regime (Vannair® 200/6 µg, 2 puffs twice a day plus Ventolin® as a reliever)

"Randomly" means it is a matter of chance (like flipping a coin), so you have a 1 in 2 chance of receiving either treatment.

You will be asked to bring all your current asthma inhalers with you to the first visit so that we can exchange your inhalers with a supply of study medication – it is important during the study that you only use the inhalers that we have supplied, so that we can get an accurate record of the number of doses of medication you have needed.

When you receive the first set of study medication you will be given a back-up inhaler so that if you have to delay your appointment or need to use more than normal for an attack, you will have enough medication to cover this situation. If you need a replacement back-up inhaler, please let the study doctor or nurse know. We will give you some written advice and information on how to care for your new inhaler(s).

Together with the inhalers that you will receive at the first study visit, we will provide you with a written Asthma Self Management Plan. There will be one plan for patients on the SMART treatment and another plan for the patients on the Standard treatment. If you currently use a Peak Flow meter, then you will receive a management plan that makes use of your peak flow readings. If you don't currently use a Peak Flow meter, then we will give you a plan that is based around your symptoms of asthma. We will discuss the plan with you so that you are satisfied with it, together with checking your inhaler technique.

Your next appointment will be booked for 3 weeks later. Please remember to bring all your own inhalers with you for the first study visit and to bring the study medication back with you to your next appointment.

What happens at the following study visits?

At the next study visits you will be asked if you have had any health problems including asthma attacks, or if you have started any new medications. The tests of your breathing will be repeated and you will complete a questionnaire about your asthma. At each visit you will need to bring your study medication with you and return it to the study co-ordinator or doctor. You will be given a new supply of medication at all the visits except the last one.

The study visits will be booked approximately 3 weeks apart for visits 1 and 2 and then 7 weeks apart for visits 3, 4 and 5 (so they will be at weeks 0, 3, 10, 17 and 24 from your starting the study). If you find that you need to change your study appointment date or time please let your study contact know as soon as possible. With your permission, we will send you a text message on your mobile phone or telephone you (whichever you prefer) 2-3 days before your study appointments, in order to check that the time and date is still convenient for you. We will try to make appointments at similar times of the day for each of your study visits where possible, so that we can better compare the readings from your spirometry.

What happens if my asthma troubles me during the study or I have an asthma attack?

The day-to-day care of your asthma with remain in the hands of your GP. We would like you to use your inhaler for relief of your asthma symptoms as you would do normally. We will provide you with a self management plan that will help to guide you if your asthma becomes troublesome or you have an asthma attack during the course of the study; this plan will make use of your peak flow readings if this is something that you currently measure.

If during the study you have an asthma attack, you should go to see your General Practitioner (GP), or go to an after-hours clinic or the hospital emergency department (ED) and seek medical care - you will receive the same care and treatment as you would do if you were not involved in the study.

Your self management plan will also provide you with guidance as to when to start a course of prednisone (steroids) for your asthma. If you usually keep a course of prednisone at home in case of an emergency, then you can continue to do this during the study and obtain any extra prescriptions from your GP. For patients who do not usually keep prednisone at home, we suggest taking a course of 40 mg a day of prednisone for 5 days, and then to stop, but this decision will be made when you see your GP. **As per your asthma self-management plan, you must seek review by a doctor when you feel your asthma is worsening and every time you start a course of prednisone.**

If you take a course of steroids for your asthma, either in tablet or liquid form or into your veins in hospital, then we would like you to make a note of the date this treatment started on the appointment reminder card that we give you, together with how many days you were treated for. This is so that we can keep a record of when your asthma has been troublesome and if necessary, obtain further information about your health from the hospital or GP records. When we see you at our study visits, we will ask you if you have taken any steroids since we last saw you or if you have been admitted to hospital/attended the Emergency Department. To make sure that we have all the information we need about the attack, we will need to contact the health service provider involved to check the medical details.

What tests and procedures will be carried out?

Spirometry
We will measure how your lungs are working by asking you to blow into a machine called a spirometer as hard as you can. This is similar to a "peak flow" and will be done at all five visits. For all the study visits, please continue to use your inhaler(s) as you would do normally.

Asthma Control Questionnaire
At each study visit you will be asked to complete a questionnaire called the Asthma Control Questionnaire – this is a simple questionnaire and will only take approximately 5 minutes. The questionnaire asks you about your asthma symptoms in last week prior to your study appointment and how much they have bothered you or limited what you could do.

Satisfaction with Inhaled Asthma Treatment Questionnaire
At the first and last study visits, you will be asked to complete a questionnaire called the Satisfaction with Inhaled Asthma Treatment Questionnaire. This will ask you about how you feel about your current asthma treatment and how convenient it is for you. The questionnaire will take approximately between 5 and 10 minutes to complete.

What are the possible risks and discomforts?

In NZ, Vannair® is registered for the treatment of asthma and is commonly used. Possible side effects include: mild irritation in the throat, coughing, hoarseness, thrush (fungal infection in mouth and throat), headache, trembling, and rapid heartbeat. Less common side effects include: sleep difficulties, restlessness, nervousness and anxiety, dizziness, nausea, and muscle cramps.

Ventolin® is also a commonly used registered medication in NZ for the treatment of asthma. Side effects with this medication usually occur at higher doses. Possible side-effects include headache, nausea, shaky or tense feelings, rapid heartbeat, a 'warm' feeling (caused by peripheral vasodilation), and mouth or throat irritation. A rare side-effect is muscle cramp.

The spirometry tests should not cause any discomfort and are very safe tests that should not present any risk to you.

There is also a chance that you might have a worsening of your asthma during the study. If this occurs you can still continue with the study if you choose to and attend the remaining visits. **Throughout your time in the study you will receive normal care from your usual doctor and we will notify your GP that you are participating. If you suffer from worsening of your asthma during your time in the study, you should contact your GP, after-hours clinic or hospital emergency department as you would do normally.**

What are the possible benefits?

We will supply your asthma medication during the trial which may save you on time and costs associated with visiting the pharmacy. Additionally, you will be contributing valuable research information that may help us to better understand the best treatments for asthma.

Will taking part cost anything?

There will be no costs to you as a result of being involved in the study. If appropriate, you will be given compensation for your travel costs to and from the study appointments.

What if I am pregnant or become pregnant during the course of the study?

Specific research looking into the effects of Vannair® in pregnancy have not been performed in the past, but the combination of budesonide and eformoterol is used currently in pregnant asthmatic patients in whom the benefits of achieving asthma control outweigh the theoretical risks of treatment. We can discuss the risks and benefits with you if you are pregnant and are thinking about entering the study or if you become pregnant during the course of the study.

Participant rights and study withdrawal

Participation in this study is entirely voluntary and you do not have to take part. Your decision whether or not to participate will not affect your health care in any way or your future relations with the hospital. During the study you will be kept informed of anything that may influence your decision to continue to participate in the research.

If you agree to participate, you may withdraw from the study at any time. If you refuse to participate or if you choose to withdraw (at any time) this will not affect your health care or any benefits to which you are otherwise entitled.

Your participation in the study may be stopped for the following reasons:

- If you are unable to follow the investigator's instructions.
- The investigator decides it is in the best interest of your health and welfare to discontinue.

Compensation for injury

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act 2001. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the Injury Prevention Rehabilitation and Compensation Act 2001. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

You are also advised to check whether participation in this study would affect any indemnity cover you have or are considering, such as medical insurance, life insurance and superannuation.

Confidentiality and data privacy

If you decide to participate in the study, the study doctor/nurse and Medical Research Institute of New Zealand staff will collect medical and personal information about you as part of doing the study.

By agreeing to take part in this research, you will allow your medical information and results to be seen by people who check that the research was done properly.

No material which could personally identify you will be used in any reports on this study. Your personal information (for example your gender, age and medical conditions) and other information will be identified by a number (i.e. coded). The study records will be stored securely in locked offices during the course of the study and archived in a secure facility for a minimum of 10 years after the study finishes. The records will then be confidentially destroyed.

Will I be able to find out the results of the study?

Yes, you will be able to find out the results of the study when it is completed.

What happens at the end of the Study?

At the final study visit, you will be placed back onto the usual asthma medication that you were taking prior to your starting on the study. If you feel that your inhaled treatment may need to be adjusted after the end of the study, then you will need to discuss this with your GP. We will inform your GP that the study has ended and that you may be planning to discuss your inhaled treatment with your GP if you feel that any adjustments need to be made.

Where can I get more information about the study?

You can call the researcher whose details are at the bottom of this information sheet. An interpreter can be provided.

Statement of Approval

This study has received ethical approval from the Multi-region Ethics Committee, which reviews national and multiregional studies, ethics reference number **MEC/09/11/127**.

Patient's Rights

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact an independent health and disability advocate:
Free phone: 0800 555 050 Free fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

Contact

If you have any questions about the study you can contact:

Study Investigator OR Principal Investigator

Dr Mitesh Patel
Telephone: Freephone 0800 25 15 25
Email: asthma.study@mrinz.ac.nz

Professor Richard Beasley
Telephone: (04) 805 0147
Email: richard.beasley@mrinz.ac.nz

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

Participant Informed Consent Form

Short Study title: A study to investigate the "real-life" use of the Vannair® "SMART" regime in patients with asthma (the SMART study)

Participant Number: _____

REQUEST FOR AN INTERPRETER

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai

Participant Initials: _____

Please tick to indicate consent to the following:

I agree to take part in the research study titled "A study to investigate the "real-life" use of the Vannair® "SMART" regime in patients with asthma (the SMART study)" and I have had time to consider participation.	☐
I have read and understand the Participant Information Sheet **version 3 dated 1 December 2010.** I have had the opportunity to discuss this study with the study investigator and have had time to consider whether or not to participate.	☐
I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.	☐
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and the information sheet.	☐
I consent to Te Hononga O Tamaki Me Hoturoa Healthcare, Clinicanz (on behalf of the study GPs in Tauranga and Auckland), Tu Kotahi Maori Asthma Trust and the Medical Research Institute of New Zealand staff collecting and processing my information, including information about my health.	☐

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 used.	☐
I agree to an approved auditor appointed by the University of Auckland, the Medical Research Institute of New Zealand, the Multi Region Ethics Committee, or a 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 taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without giving a reason. This will not affect my continuing health care.	☐
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 that my involvement in this study will be stopped if it should appear to be harmful.	☐
I understand that where appropriate I will receive compensation for travel costs upon completion of the trial and that this amount may be reduced if I do not complete the trial.	☐
I know who to contact if I have any side effects or if anything occurs which would be a reason to withdraw from the study.	☐
I agree to my GP being notified of my participation in this study.	☐
I agree to the researchers contacting the relevant health service providers to request details about any asthma exacerbations I have during the study.	☐
I agree to the researchers contacting me by telephone or text messaging via mobile phone in order to communicate appointment times or issues relating directly to this study.	☐
I would like to be advised of the study results.	YES/NO

This project has been approved by the Multi-region Ethics Committee. This means that the Committee may check that this study is running smoothly and that the study has followed appropriate ethical procedures. If you have any concerns about the study, you may contact the Multi-regional Ethics Committee on (04) 470 0655.

Statement by Participant: ***I hereby consent to take part in this study.***

Name of Participant: _____ Date of Birth: _____

Signature of Participant: _____ Date: _____

Statement by Investigator: ***I have fully explained and discussed with the participant the nature, purpose, demands (and possible effects) of the study***

Name of Investigator/Co-investigator: _____

Signature of Investigator/Co-Investigator: _____

Date: _____

APPENDIX C: PATIENT INFORMATION

Care of the inhaler sheet

Patient appointment card/exacerbation record card

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

GUIDANCE ON THE CARE OF YOUR NEW INHALER DEVICE

During your involvement with this study, you will be provided with an **inhaler that is fitted with a small electronic device** that is able to record the number of doses of drug that has been used. We wish to make sure that the inhaler works as accurately as possible and we would be grateful if you could bear the following in mind:

1. **Your inhaler must not be immersed in water, or washed, as it contains an electronic device that will be damaged by water.**
2. Please keep the inhaler free of chemicals, steam and damp surroundings.
3. Please do not remove or change the medication canister that inserted into the plastic inhaler as this may affect the data that is collected.
4. **Please do not use non-study inhalers while you are involved with this study or share your inhalers with friends/family members/whanau. Please also do not perform 'test puffs' prior to using your inhaler.**

What if I need to clean my study inhaler?

If you need to clean your inhaler, please do so by wiping the outside plastic casing with a **lightly dampened cloth** and then leaving it to dry naturally at room temperature.

What if my inhaler gets damaged/gets wet/does not seem to be working?

Your inhaler will be tested prior to being given to you to check that it is working accurately. If at any time you have concerns that it may not be functioning correctly, please use one of the other study inhalers that has been given to you and speak with your Study Contact. They will be able to give you advice on what to do next. **Please do not throw away your inhaler, even if it does not seem to be working, as we will need to check its function after you return it to us.**

What if I run out of inhalers before my next study visit?

We have aimed to provide you with sufficient inhalers to last until your next study visit, together with 1 'emergency use/backup' inhaler. Please keep your backup inhaler sealed in its envelope in a safe place. If, however, you are down to using your last inhaler and are likely to need more before your next study visit, or need a new backup inhaler, please contact your Study Contact as soon as possible so that they can arrange for more to be provided for you.

Are there any other special instructions on how to use my study inhaler?

Your inhaler works like any other pressurized Metered Dose Inhaler (pMDI) and does not require any other special instructions for its use. Your study contact will show you how to get the best out of your inhaler at your first study visit and will be able to answer any questions that you may have at your other visits.

What happens with the inhalers at the study visits?

It is very important that you bring all your inhalers with you to your study visits as they will all be collected from you each time and exchanged for inhalers with new canisters of medication in them. We will keep track of the plastic outer casings so that you will get your own ones back at future visits. The data on the inhalers will provide important information to us about your asthma.

Remember - please try & care for your inhaler as you would do any small electronic device (e.g. your mobile phone)

Study Contact: Contact Tel:

SMART appointment card, Version 2, 12 April 2010

After Hours Emergency Contact:	**Study Contact:**
In case of an asthma attack, please see your GP or go to the After Hours or Emergency Department. A/Hours: Wellington Accident & Urgent Medical Centre Ph: (04) 384 4944 Wellington Hospital Ph: (04) 385 5999 **Ambulance:** **Dial 111**	Dr Mitesh Patel Medical Research Institute of New Zealand Level 7, CSB Building Wellington Hospital Riddiford Street Newtown Wellington 6021 Ph: 0800 25 15 25 Fax: (04) 389 5707 Email: asthma.study@mrinz.ac.nz MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

(Insert name)

_____

is an asthmatic who is involved in a 6-month research trial. He/She is receiving inhaled Vannair® 200/6 µg (budesonide+formoterol) 2 puffs twice a day with extra doses of this as a reliever.

In case of an asthma attack, please treat in accordance with standard practice.

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

SMART appointment card, Version 2, 12 April 2010

Visit 1	
Visit 2	
Visit 3	
Visit 4	
Visit 5	

	Date of prednisone prescription	**Via GP?**	**Via after hours?**	**Via ED?**	**Self?**
1					
2					
3					
4					
5					

Standard appointment card, version 2, 12 April 2010

After Hours Emergency Contact:	Study Contact:
In case of an asthma attack, please see your GP or go to the After Hours or Emergency Department. A/Hours: Wellington Accident & Urgent Medical Centre Ph: (04) 384 4944 Wellington Hospital Ph: (04) 385 5999 **Ambulance:** **Dial 111**	Dr Mitesh Patel Medical Research Institute of New Zealand Level 7, CSB Building Wellington Hospital Riddiford Street Newtown Wellington 6021 Ph: 0800 25 15 25 Fax: (04) 389 5707 Email: asthma.study@mrinz.ac.nz MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

(insert name)

_____

is an asthmatic who is involved in a 6-month research trial. He/She is receiving inhaled Vannair® 200/6 µg (budesonide+formoterol) 2 puffs twice a day with Ventolin® as a reliever.

In case of an asthma attack, please treat in accordance with standard practice.

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

Standard appointment card, version 2, 12 April 2010

Visit 1	
Visit 2	
Visit 3	
Visit 4	
Visit 5	

	Date of prednisone prescription	Via GP?	Via after hours?	Via ED?	Self?
1					
2					
3					
4					
5					

APPENDIX D: VANNAIR AND VENTOLIN MEDICINE DATA SHEETS

NEW ZEALAND DATA SHEET

NAME OF MEDICINE

VANNAIR® 100/6
VANNAIR® 200/6

Budesonide / Eformoterol fumarate dihydrate (100/6 µg or 200/6 µg per inhalation)

PRESENTATION

VANNAIR is a pressurised metered dose inhaler, comprising an internally coated aluminium can, sealed with a metering valve and fitted into a plastic actuator.

VANNAIR 100/6

VANNAIR 100/6 pMDI delivers the same amount of budesonide and eformoterol as Symbicort Turbuhaler®100/6.

Each delivered dose (the dose that leaves the mouthpiece) of VANNAIR 100/6 pMDI contains as active constituents: budesonide 80 micrograms/inhalation and eformoterol fumarate dihydrate 4.5 micrograms/inhalation.

Each inhaler contains 120 inhalations.

VANNAIR 200/6

VANNAIR 200/6 pMDI delivers the same amount of budesonide and eformoterol as Symbicort Turbuhaler 200/6.

Each delivered dose (the dose that leaves the mouthpiece) of VANNAIR 200/6 pMDI contains as active constituents: budesonide 160 micrograms/inhalation and eformoterol fumarate dihydrate 4.5 micrograms/inhalation.

Each inhaler contains 120 inhalations.

Eformoterol fumarate dihydrate is hereafter referred to as eformoterol.

INDICATIONS

Asthma

VANNAIR pMDI is indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting $beta_2$-agonist) is appropriate. This includes:

- Patients who are not adequately controlled with inhaled corticosteroid therapy and "as needed" inhaled short-acting beta-2 adrenoceptor agonists.
- Patients who are already adequately controlled on regular separate long acting beta-agonist and inhaled corticosteroid therapies.

DOSAGE AND ADMINISTRATION

The dosage of VANNAIR pMDI should be individualised according to disease severity. When control has been achieved, the dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

ASTHMA

The patients should be instructed that VANNAIR pMDI must be used even when asymptomatic for optimal benefit.

Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants reassessment of the asthma therapy.

Adults and adolescents (12 years and older):

VANNAIR 100/6: 2 inhalations once or twice daily.
Maximum daily maintenance dose: 4 inhalations

VANNAIR 200/6: 2 inhalations once or twice daily.
Maximum daily maintenance dose: 4 inhalations

In some cases, up to a maximum of 4 inhalations twice daily may be required as maintenance dose or temporarily during worsening of asthma.

Children (6-11 years)

VANNAIR 100/6: 2 inhalations twice daily.
Maximum daily dose: 4 inhalations

Children under 6 years of age:

The use of VANNAIR is not recommended in children under six years of age.

Special Populations

There are no special dosing requirements for elderly patients.

There are no data available for use of VANNAIR in patients with hepatic or renal impairment. As budesonide and eformoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver diseases.

INSTRUCTIONS FOR CORRECT USE OF VANNAIR pMDI

On actuation of VANNAIR pMDI, a volume of the suspension is expelled from the canister at high velocity. When the patient inhales through the mouthpiece at the same time as actuating the inhaler, the substance will follow the inspired air into the airways.

Note It is important to instruct the patient to:

- carefully read the instructions for use in the patient information leaflet which is packed together with each inhaler.
- shake the inhaler gently prior to each use to mix its contents properly.
- prime the inhaler by actuating it twice into the air when the inhaler is new or has not been used for more than one week or if it has been dropped.
- place the mouthpiece in the mouth. While breathing in slowly and deeply, press the device firmly to release the medication. Continue to breathe in and hold the breath for approximately 10 seconds or as long as is comfortable.
- shake the inhaler again and repeat.
- rinse the mouth with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush.
- clean the mouthpiece of the inhaler regularly, at least once a week with a clean dry cloth.
- do not put the inhaler into water.

CONTRAINDICATIONS

Hypersensitivity (allergy) to budesonide, eformoterol or any of the excipients.

WARNINGS AND PRECAUTIONS

DOSING AND DISCONTINUATION

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

Therapy with VANNAIR should not be initiated during a severe exacerbation or if patients have significantly worsening or acutely deteriorating asthma.

The lowest effective dose of VANNAIR should be used.

Patients should be reminded to take their VANNAIR maintenance dose as prescribed, even when asymptomatic. They should also be advised to have their rescue inhaler available at all times.

VANNAIR should not be taken in response to asthma symptoms. For such use, a separate rapid-acting bronchodilator should be considered.

If the patient finds the treatment ineffective or exceeds the prescribed dose of VANNAIR pMDI, the patient should be reviewed by a physician.

Once asthma symptoms are controlled, consideration may be given to stepping down treatment with VANNAIR. Regular review of patients as treatment is stepped down is important.

When long-term treatment with VANNAIR is to be discontinued, the dose should be tapered. Treatment should not be stopped abruptly.

DETERIORATION OF ASTHMA CONTROL

Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control.

Sudden and progressive deterioration in control of asthma is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids, e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present.

Patients should be advised to seek medical attention if sudden deterioration of their asthma occurs, or if they find that short-acting relief bronchodilator treatment becomes less effective.

ASTHMA EXACERBATIONS

Serious asthma-related adverse events and exacerbations may occur during treatment with VANNAIR. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after inhalation of VANNAIR.

VANNAIR must not be initiated or the dose increased during an asthma exacerbation.

POTENTIAL SYSTEMIC EFFECTS OF INHALED CORTICOSTEROIDS

VANNAIR contains an inhaled corticosteroid (budesonide).

VANNAIR should not be used to initiate treatment with inhaled corticosteroids in patients being transferred from oral steroids.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. However, these effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur.

Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity.

Therefore it is important that the patient is reviewed regularly and the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

HPA AXIS SUPPRESSION AND ADRENAL INSUFFICIENCY

Dose-dependent HPA axis suppression (as indicated by 24 hour urinary and/or plasma cortisol AUC) has been observed with inhaled budesonide, although the physiological circadian rhythms of plasma cortisol were preserved. This indicates that the HPA axis suppression represents a physiological adaptation in response to inhaled budesonide, not necessarily adrenal insufficiency. The lowest dose that results in clinically relevant adrenal insufficiency has not been established. Very rare cases of clinically relevant adrenal dysfunction have been reported in patients using inhaled budesonide at recommended doses.

Clinically important disturbances of the HPA axis and/or adrenal insufficiency induced by severe stress (e.g. trauma, surgery, infection in particular gastroenteritis or other conditions associated with severe electrolyte loss) may be related to inhaled budesonide in specific patient populations. These are patients with prolonged treatment at the highest recommended dose of VANNAIR and patients administered concomitant CYP3A4-inhibitors (see INTERACTIONS). Monitoring for signs of adrenal dysfunction is advisable in these patient groups. For these patients additional systemic glucocorticosteroid cover should be considered during periods of stress, a severe asthma attack or elective surgery.

Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients who have required high-dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Care should be taken when commencing VANNAIR treatment, particularly if there is any reason to suspect that adrenal function is impaired from previous systemic steroid therapy.

BONE DENSITY

Whilst corticosteroids may have an effect on bone mass at high doses, studies with budesonide treatment in adults at recommended doses, have not demonstrated any significant effect on bone mineral density. No information regarding the effect of VANNAIR at higher doses is available.

Bone mineral density measurements in children should be interpreted with caution as an increase in bone area in growing children may reflect an increase in bone volume. In three large medium to long term (12 months - 6 years) studies in children (5-16 years), no effects on bone mineral density were observed after treatment with budesonide (189 - 1322μg/day) compared to nedocromil, placebo or age matched controls. However, in a randomised 18 month study (n=176; 5-10 years), bone mineral density was significantly decreased by 0.11 g/cm^2 (p=0.023) in the group treated with inhaled budesonide via Turbuhaler compared with the group treated with inhaled disodium cromoglycate. The dose of budesonide was 400μg bd for 1 month, 200μg bd for 5 months and 100μg bd for 12 months and the dose of disodium cromoglycate 10mg tid. The clinical significance of this result remains uncertain.

GROWTH

Long term studies suggest that children and adolescents treated with inhaled budesonide ultimately achieve their adult target height. However an initial small but transient reduction in growth (approx 1 cm) has been observed. This generally occurs within the first year of treatment.

It is recommended that the height of children and adolescents receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible.

Physicians should carefully weigh the benefits of the corticosteroid therapy against the possible risks of growth suppression.

OROPHARYNGEAL CANDIDA INFECTION

Candida infection in the oropharynx has been reported due to drug deposition in association with inhalation therapy. To minimise the risk of oropharyngeal candida infection, the patient should be instructed to rinse their mouth out with water after inhaling the maintenance dose. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroids.

PARADOXICAL BRONCHOSPASM

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath after dosing. If the patient experiences paradoxical bronchospasm, VANNAIR should be discontinued immediately, the patient should be assessed, and an alternative therapy instituted if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway.

PATIENTS WITH OTHER MEDICAL CONDITIONS

Infections / Tuberculosis

Signs of existing infection may be masked by the use of high doses of glucocorticosteroids and new infections may appear during their use.

As with all inhaled medication containing corticosteroids, VANNAIR should be administered with caution in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

Sensitivity to sympathomimetic amines

In patients with increased susceptibility to sympathomimetic amines (e.g. inadequately controlled hyperthyroidism), eformoterol should be used with caution.

Thyrotoxicosis

VANNAIR pMDI should be administered with caution in patients with thyrotoxicosis.

Cardiovascular disorders

β_2-agonists have an arrhythmogenic potential that must be considered before commencing treatment for bronchospasm. Cardiovascular effects, such as increases in systolic blood pressure and heart rate, may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses.

The effects of eformoterol in acute as well as chronic toxicity studies were seen mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These are known pharmacological manifestations seen after administration of high doses of β_2-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions may be at greater risk of developing adverse cardiovascular effects following administration of β_2-adrenoreceptor agonists. Caution is advised when eformoterol is administered to patients with severe cardiovascular disorders such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

QTc-interval prolongation

Caution should be observed when treating patients with prolongation of the QTc-interval. Eformoterol itself may induce prolongation of the QTc-interval.

Hypokalaemia

VANNAIR should be administered with caution in patients predisposed to low levels of serum potassium.

High doses of β_2-agonists can lower serum potassium by inducing a redistribution of potassium from the extracellular to the intracellular compartment, via stimulation of Na^+/K^+-ATPase in muscle cells. Potentially serious hypokalaemia may result.

Concomitant treatment of beta-2 adrenoceptor agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta-2 adrenoceptor agonist.

Particular caution is advised in unstable or acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments (see INTERACTIONS). Patients receiving digoxin are particularly sensitive to hypokalaemia. Serum potassium levels should therefore be monitored in such situations.

Diabetes mellitus

VANNAIR should be administered with caution in patients with diabetes mellitus.

Due to the blood-glucose increasing effects of β_2- stimulants extra blood glucose controls are initially recommended when diabetic patients are commenced on eformoterol.

DRUG INTERACTION POTENTIAL

Concomitant treatment with ritonavir, itraconazole, ketoconazole or other potent CYP3A4 inhibitors should be avoided (see INTERACTIONS). If this is not possible, the time interval between administration of the interacting drugs should be as long as possible.

In vivo studies have shown that oral administration of ketoconazole or itraconazole (known inhibitors of CYP3A4 activity in the liver and in the internal mucosa, also see INTERACTIONS) may cause an increase of the systemic exposure to budesonide, and consequently lead to systemic adverse reactions, such as Cushing's Syndrome. This is of limited importance for short-term (1-2 weeks) treatment, but should be taken into consideration during long-term treatment.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES

VANNAIR pMDI is not expected to adversely affect the ability to drive or use machines.

USE IN PREGNANCY AND LACTATION

Pregnancy

VANNAIR should only be used in pregnancy if the potential benefits outweigh the potential risks to the foetus. Only after special consideration should VANNAIR be used during the first 3 months and shortly before delivery.

VANNAIR should be used during labour only if the potential benefit justifies the potential risk.

For VANNAIR pMDI or the concomitant treatment with budesonide and eformoterol no clinical data on exposed pregnancies are available. Data from an embryo-fetal development study in the rat, showed no evidence of any additional effect from the combination.

In animal studies eformoterol has caused adverse effects in reproduction studies at very high systemic exposure levels (see PHARMACEUTICAL PROPERTIES – Pre-Clinical Safety Data). Data on approximately 2500 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide.

Lactation

Administration of VANNAIR pMDI to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Budesonide is excreted in breast milk; however, due to the relatively low doses used via the inhaled route, the amount of drug present in the breast milk, if any, is likely to be low. Consequently, no effects due to budesonide are anticipated in breast-fed children whose mothers are receiving therapeutic doses of VANNAIR.

It is not known whether eformoterol passes into human breast milk. In rats, small amounts of eformoterol have been detected in maternal milk.

INTERACTIONS

Budesonide and eformoterol have not been observed to interact with any other medicines used in the treatment of asthma.

EFORMOTEROL

Beta-receptor blocking agents:

Beta-receptor blocking agents (including eye drops), especially those that are non-selective, may partially or totally inhibit the effect of β_2-agonists, such as eformoterol. These medicines may also increase airway resistance. Therefore the use of these medicines in asthma patients is not recommended.

Other sympathomimetic agents:

Other β-adrenergic stimulants or sympathomimetic amines such as ephedrine should not be given concomitantly with eformoterol, since the effects will be cumulative. Patients who have already received large doses of sympathomimetic amines should not be given eformoterol.

Xanthine derivatives, mineralocorticosteroids and diuretics:

Hypokalaemia may result from β_2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, mineralocorticosteroids, and diuretics such as thiazides and loop diuretics (see WARNINGS AND PRECAUTIONS - HYPOKALAEMIA section).

Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines:

The adverse cardiovascular effects of eformoterol may be exacerbated by concurrent administration of medicines associated with QT interval prolongation. For this reason caution is advised when eformoterol is administered to patients already taking monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines or antihistamines associated with QT interval prolongation (eg terfenadine, astemizole) as these can prolong the QTc-interval and increase the risk of cardiovascular effects such as ventricular arrhythmias.

L-Dopa, L-thyroxine, oxytocin and alcohol:

L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β_2-sympathomimetics.

BUDESONIDE

CYP3A4 inhibitors

The metabolism of budesonide is primarily mediated by CYP3A4. Inhibitors of this enzyme, e.g. ketoconazole and itraconazole, may therefore increase plasma levels

and thus systemic exposure to budesonide (see WARNINGS AND PRECAUTIONS). The concomitant use of these medicines should be avoided unless the benefit outweighs the increased risk of systemic side effects.

At recommended doses, cimetidine has a slight but clinically insignificant effect and omeprazole has no effect on the pharmacokinetics of oral budesonide.

ADVERSE EFFECTS

Since VANNAIR pMDI contains both budesonide and eformoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side effects of $beta_2$-agonist therapy, such as tremor and palpitations. These tend to be mild and disappear within a few days of treatment.

Adverse reactions, which have been associated with budesonide and/or eformoterol, are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1000) and very rare (< 1/10 000).

Adverse Drug Reactions by frequency and system organ class (SOC)

Common	*Cardiac disorders:*	Palpitations
	Infections and infestations:	Candida infections in oropharynx
	Nervous system disorders:	Headache, tremor
	Respiratory, thoracic and mediastinal disorders:	Mild irritation in the throat Coughing Hoarseness
Uncommon	*Cardiac disorders:*	Tachycardia
	Gastrointestinal disorders:	Nausea, diarrhoea
	Metabolism and nutrition disorders	Weight gain
	Musculoskeletal and connective tissue disorders:	Muscle cramps
	Nervous system disorders:	Dizziness, taste disturbances, thirst, tiredness
	Psychiatric disorders:	Agitation, restlessness, nervousness, sleep disturbances
Rare	*Cardiac disorders:*	Cardiac arrhythmias, e.g.atrial fibrillation, supraventricular tachycardia,

		extrasystoles
	Immune system disorders:	Immediate and delayed hypersensitivity reactions, e.g. dermatitis, exanthema, urticaria, pruritus, angioedema and anaphylactic reaction
	Respiratory, thoracic and mediastinal disorders:	Bronchospasm
	Skin and subcutaneous tissue disorders:	Skin bruising
	Metabolism and nutrition disorders	Hypokalaemia
Very rare	*Cardiac disorders:*	Angina pectoris Prolongation of the QTc-interval
	Endocrine disorders:	Signs or symptoms of systemic glucocorticosteroid effects, e.g. Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density
	Eye disorders	Cataract Glaucoma
	Metabolism and nutrition disorders:	Hyperglycaemia
	Psychiatric disorders:	Anxiety Depression Behavioural disturbances
	Vascular disorders	Variations in blood pressure

Treatment with beta-2 adrenoceptor agonists may also result in an increase in blood levels of insulin, free fatty acids, glycerol, and ketone bodies.

OVERDOSAGE

EFORMOTEROL

An overdose of eformoterol would likely lead to effects that are typical for beta$_2$-adrenoceptor agonists: tremor, headache, palpitations. . Hypotension, metabolic acidosis, prolonged QTc-interval, arrhythmia, nausea, vomiting, hypokalaemia and hyperglycaemia may also occur.

Supportive and symptomatic treatment may be indicated. Beta-blockers should be used with care because of the possibility of inducing bronchospasm in sensitive individuals.

If VANNAIR therapy has to be withdrawn due to overdose of the eformoterol component of the drug, provision of appropriate inhaled corticosteroid therapy must be considered.

BUDESONIDE

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects may appear, such as hypercorticism and adrenal suppression.

PHARMACEUTICAL PROPERTIES

Pharmacodynamic properties

VANNAIR contains budesonide and eformoterol, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations. The respective mechanisms of action of both drugs are discussed below.

Budesonide

Budesonide is a glucocorticosteroid which when inhaled has a rapid (within hours) and dose dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer asthma exacerbations. Inhaled budesonide has less severe adverse effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

Eformoterol

Eformoterol is a selective $beta_2$-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

Pharmacokinetics

Absorption:

Symbicort® Turbuhaler (a dry powder inhaler containing budesonide and eformoterol) and the corresponding monoproducts (Pulmicort® Turbuhaler and Oxis® Turbuhaler, respectively) have been shown to be bioequivalent with regard to systemic exposure of budesonide and eformoterol, respectively.

In addition, the pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and eformoterol as monoproducts or as Symbicort® Turbuhaler. Thus, there was no evidence of pharmacokinetic interactions between budesonide and eformoterol when given together.

Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation.

Inhaled eformoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation.

Distribution and Metabolism

Plasma protein binding is approximately 50% for eformoterol and 90% for budesonide. Volume of distribution is about 4 L/kg for eformoterol and 3 L/kg for budesonide. Eformoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6 beta-hydroxy-budesonide and 16α-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between eformoterol and budesonide.

Elimination:

The major part of a dose of eformoterol is eliminated by metabolism in the liver followed by renal excretion. After inhalation of eformoterol via Turbuhaler, 8% to 13% of the delivered dose of eformoterol is excreted unmetabolised in the urine. Eformoterol has a high systemic clearance (approximately 1.4 L/min) and the terminal elimination half-life averages 17 hours.

Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are excreted in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma elimination half-life after i.v. dosing averages 4 hours.

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 year old asthmatic children. Per kg body weight children have a clearance, which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. The pharmacokinetics of eformoterol in children has not been studied.

The pharmacokinetics of budesonide or eformoterol in elderly and in patients with renal failure is unknown. The exposure of budesonide and eformoterol may be increased in patients with liver disease.

PRECLINICAL SAFETY DATA

The toxicity observed in animal studies with budesonide and eformoterol was similar whether budesonide or eformoterol were given in combination or separately. The effects were associated with pharmacological actions and dose dependent.

In animal reproduction studies, glucocorticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant in humans at the recommended doses (see WARNINGS AND PRECAUTIONS – Pregnancy and Lactation). Animal reproduction studies with eformoterol have shown a somewhat reduced fertility in male rats at high systemic exposure and implantation losses, as

well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. However, these animal experimental results do not seem to be relevant to man.

VANNAIR pMDI contains the excipients povidone (polyvinylpyrrolidone) K25, macrogol (polyethylene glycol) 1000 and the pressurised liquid propellant apaflurane (HFA 227). The safe use of apaflurane has been fully evaluated in preclinical studies. Povidones have a history of safe use in man for many years, which supports the view that povidones are essentially biologically inert. Macrogols are recognised as safe excipients in pharmaceuticals, food and cosmetic products. Furthermore, toxicity studies carried out using VANNAIR pMDI have shown no evidence of any local or systemic toxicity or irritation attributable to the excipients.

CLINICAL EFFICACY

VANNAIR pMDI

Clinical comparability was demonstrated by a long-term safety study, which showed that the safety profile and tolerability of VANNAIR pMDI were similar to that of Symbicort Turbuhaler.

Symbicort Turbuhaler

Clinical studies have shown that the addition of eformoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. The effect on lung function of Symbicort Turbuhaler was equal to that of the free combination of budesonide and eformoterol in separate inhalers in adults and exceeded that of budesonide alone in adults and children. The free combination of budesonide and eformoterol does not mask the onset or severity of exacerbations. There was no sign of attenuation of the anti-asthmatic effect over time.

Symbicort Turbuhaler has been proven in clinical trials to improve patient symptoms, reduce the use of short-acting reliever medication and increase asthma control when compared to inhaled corticosteroid treatment alone. Furthermore, eformoterol and budesonide in separate inhalers have been shown to reduce nocturnal awakenings, decrease the rate of exacerbations and improve the quality of life.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS

- Apaflurane (HFA 227)
- Povidone K25
- Macrogol (polyethylene glycol) 1000

STORAGE CONDITIONS

Do not store above 30°C.

SHELF-LIFE

The shelf life for VANNAIR pMDI as packaged for sale is 2 years. The shelf life after first opening is 3 months.

CONTAINER

A pressurised container, comprising of an internally coated aluminium can, sealed with a metering valve and fitted into a plastic actuator. Each inhaler delivers 120 actuations of budesonide/eformoterol 80/4.5 or 160/4.5 micrograms (delivered dose) after initial priming. Each inhaler is individually wrapped in a foil laminate pouch containing a desiccant.

INSTRUCTIONS FOR USE

See DOSAGE AND ADMINISTRATION and the Consumer Medicine Information.

The canister should not be broken, punctured or burnt, even when apparently empty.

The canister contains a pressurised liquid. Do not expose to temperatures above 50°C.

INCOMPATABILITIES

Not applicable.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Each inhaler contains 120 actuations.

NAME AND ADDRESS

AstraZeneca Limited
Level 5, 15 Hopetoun Street,
Freemans Bay Auckland 1011.
P299 Private Bag 92175, Auckland 1142
Telephone: (09) 306 5650

DATE OF PREPARATION

31 October 2011
CDS 091007

DATA SHEET

Ventolin Inhaler (CFC-Free)

Salbutamol (as sulphate) Inhaler (CFC-free) 100mcg per actuation.

Qualitative and quantitative composition

Ventolin Inhaler (CFC-Free) comprises a suspension of salbutamol sulphate in the non-CFC propellant HFA 134a. The suspension is contained in an aluminium alloy can, internally coated with fluoropolymer and sealed with a metering valve. Each canister is fitted with a plastic actuator incorporating an atomising nozzle and fitted with a dustcap.

Ventolin Inhaler (CFC-Free) is a pressurised metered-dose inhaler which delivers 100μg salbutamol (as sulphate) per actuation, into the mouthpiece of a specially designed actuator. The inhaler also contains the CFC-free propellant HFA134a. Each canister contains at least 200 actuations.

Pharmaceutical form

Pressurised metered-dose aerosol.

Clinical particulars

Therapeutic Indications

Salbutamol is a selective β_2 adrenoceptor agonist. At therapeutic doses it acts on the β_2 adrenoceptors of bronchial muscle, with little or no action on the β-1 adrenoceptors of the heart. With its fast onset of action, it is particularly suitable for the management and prevention of attack in mild asthma and for the treatment of acute exacerbations in moderate and severe asthma.

Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment as death may occur. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60% predicted at baseline with greater than 30% variability, usually not returning entirely to normal after a bronchodilator. These patients will require high dose inhaled (e.g >1mg/day beclomethasone dipropionate) or oral corticosteroid therapy.

With this primary background corticosteroid treatment, Ventolin provides essential rescue medication for a severe asthmatic in treating acute exacerbations. Failure to respond promptly or fully to such rescue medication signals a need for urgent medical advice and treatment.

Salbutamol provides short-acting (4 hour) bronchodilation with fast onset (within 5 minutes) in reversible airways obstruction due to asthma, chronic bronchitis and emphysema. It is suitable for long-term use in the relief and prevention of asthmatic symptoms.

Ventolin should be used to relieve symptoms when they occur and to prevent them in those circumstances recognised by the patient to precipitate an asthmatic attack (e.g. before exercise or unavoidable allergen exposure).

Ventolin is particularly valuable as rescue medication in mild, moderate or severe asthma, provided that reliance on it does not delay the introduction and use of regular inhaled corticosteroid therapy.

Posology and Method of Administration

Ventolin Inhaler (CFC-Free) is administered by the oral inhaled route only, to be breathed in through the mouth.

Salbutamol has a duration of action of 4 to 6 hours in most patients.

Increasing use of β_2 agonists may be a sign of worsening asthma. Under these conditions a reassessment of the patient's therapy plan may be required and concomitant glucocorticosteroid therapy should be considered.

In patients who find co-ordination of a pressurised metered-dose inhaler difficult a spacer device may be used with the Ventolin Inhaler (CFC-Free).

Babies and young children may benefit from use of a spacer device with the Ventolin Inhaler (CFC-Free).

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice.

<u>Relief of acute bronchospasm:-</u>
Adults: 100 or 200μg.
Children: 100μg, the dose may be increased to 200μg if required.

<u>Prevention of allergen or exercise-induced bronchospasm:-</u>
Adults: 200μg before challenge
Children: 100μg before challenge, the dose may be increased to 200μg if required.

<u>Chronic therapy:-</u>
Adults: Up to 200μg four times daily

Children: Up to 200μg four times daily

On demand use of Ventolin should not exceed four times daily. Reliance on such supplementary use or a sudden increase in dose indicates deteriorating asthma (see Special Warnings and Special Precautions for Use).

Contra-indications

Ventolin Inhaler (CFC-Free) is contra-indicated in patients with a history of hypersensitivity to any of its components.

Although intravenous salbutamol and occasionally salbutamol tablets are used in the management of premature labour uncomplicated by conditions such as placenta praevia, ante-partum haemorrhage or toxaemia of pregnancy, inhaled salbutamol presentations are not appropriate for managing premature labour. Salbutamol preparations should not be used for threatened abortion.

Special Warnings and Special Precautions for Use

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

Increasing use of short-acting inhaled β_2 agonists to control symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. In patients considered at risk, daily peak flow monitoring may be instituted.

In the event of a previously effective dose of inhaled salbutamol failing to give relief for at least three hours, the patient should be advised to seek medical advice in order that any necessary additional steps may be taken.

Patients' inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of the drug to the lungs.

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

Potentially serious hypokalaemia may result from β_2 agonist therapy mainly from parenteral and nebulised administration.

Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and by hypoxia. It is recommended that serum potassium levels are monitored in such situations.

Interaction with Other Medicaments and Other Forms of Interaction

Salbutamol and non-selective β-blocking agents, such as propranolol, should not usually be prescribed together.

Salbutamol is not contra-indicated in patients under treatment with monoamine oxidase inhibitors (MAOIs).

Pregnancy and Lactation

Administration of medicines during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

During worldwide marketing experience, rare cases of various congenital anomalies, including cleft palate and limb defects have been reported in the offspring of patients being treated with salbutamol. Some of the mothers were taking multiple medications during their pregnancies.

Because no consistent pattern of defects can be discerned, and baseline rate for congenital anomalies is 2-3%, a relationship with salbutamol use cannot be established.

As salbutamol is probably secreted in breast milk its use in nursing mothers is not recommended unless the expected benefits outweigh any potential risk. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

Effects on ability to drive and use machines

None reported.

Undesirable Effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common and common events were generally determined from clinical trial data. Rare and very rare events were generally determined from spontaneous data.

Immune system disorders

Very rare: Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse.

Metabolism and nutrition disorders

Rare: Hypokalaemia.

Potentially serious hypokalaemia may result from beta$_2$ agonist therapy.

Nervous system disorders

Common: Tremor, headache.

Very rare: Hyperactivity.

Cardiac disorders

Common: Tachycardia.

Uncommon: Palpitations.

Very rare: Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles.

Vascular disorders

Rare: Peripheral vasodilatation.

Respiratory, thoracic and mediastinal disorders

Very rare: Paradoxical bronchospasm.

As with other inhalation therapy, *paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator. Ventolin Inhaler (CFC-free) should be discontinued immediately, the patient assessed, and, if necessary, alternative therapy instituted.

Gastrointestinal disorders

Uncommon: Mouth and throat irritation.

Musculoskeletal and connective tissue disorders

Uncommon: Muscle cramps.

*Tachycardia may occur in some patients.

Overdose

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see Special Warnings and Special Precautions for Use and Undesirable Effects).

Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored.

Consideration should be given to discontinuation of treatment and appropriate symptomatic treatment such as a cardioselective β-blocking agent, in patients presenting with cardiac symptoms (e.g. tachycardia, palpitations). Beta-blocking agents should be used with caution in patients with a history of bronchospasm.

Pharmacological properties

Pharmacodynamic properties

Salbutamol is a selective β_2 adrenoceptor agonist. At therapeutic doses it acts on the β_2 adrenoceptors of bronchial muscle, with little or no action on the β-1 adrenoceptors of cardiac muscle.

Pharmacokinetic properties

Salbutamol administered intravenously has a half-life of 4 to 6 hours and is cleared partly renally and partly by metabolism to the inactive 4'-O- sulphate (phenolic sulphate) which is also excreted primarily in the urine. The faeces are a minor route of excretion. The majority of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours. Salbutamol is bound to plasma proteins to the extent of 10%.

After administration by the inhaled route between 10 and 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is deposited in the oropharynx from where it is swallowed. The fraction deposited in the airways is absorbed into the pulmonary tissues and circulation but is not metabolised by the lung.

On reaching the systemic circulation it becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged salbutamol and as the phenolic sulphate.

The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulphate. Both unchanged salbutamol and conjugate are excreted primarily in the urine.

Preclinical safety data

In common with other potent selective β_2 receptor agonists, salbutamol has been shown to be teratogenic in mice when given subcutaneously. In a reproductive study, 9.3% of foetuses were found to have cleft palate, at 2.5 mg/kg, 4 times the maximum human oral dose. In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50mg/kg/day orally throughout pregnancy resulted in no significant foetal abnormalities. The only toxic effect was an increase in neonatal mortality at the highest dose level as the result of lack of maternal care. A reproductive study in rabbits revealed cranial malformations in 37% of foetuses at 50mg/kg/day, 78 times the maximum human oral dose.

HFA 134a has been shown to be non-toxic at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

Pharmaceutical particulars

List of excipients

1,1,1,2-tetrafluoroethane (also known as HFA 134a or norflurane).

Incompatibilities

None reported.

Shelf Life

24 months

Special precautions for storage

Replace the mouthpiece cover firmly and snap it into position.

Ventolin Inhaler (CFC-Free) should be stored below 30°C.

Protect from frost and direct sunlight.

As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.

The canister should not be broken, punctured or burnt, even when apparently empty.

Nature and contents of container

Ventolin Inhaler (CFC-Free) comprises a suspension of salbutamol sulphate in the non-CFC propellant HFA 134a. The suspension is contained in an aluminium alloy can, sealed with a metering valve. Each canister is fitted with a plastic actuator incorporating an atomising nozzle and fitted with a dustcap. Ventolin Inhaler (CFC-Free) delivers 100μg of salbutamol (as sulphate) per actuation.

Each canister contains at least 200 actuations.

Instructions for Use/Handling

Testing your inhaler:-

Before using for the first time remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, and release two puffs into the air to make sure that it works. If it has not been used for 5 days or more, shake it well and release two puffs into the air to make sure that it works.

Using your inhaler:-

1. Remove the mouthpiece cover by gently squeezing the sides of the cover.

2. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.

3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.

4. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece.

5. Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it.

6. Just after starting to breathe in through your mouth press down on the top of the inhaler to release salbutamol while still breathing in steadily and deeply.

7. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. Continue holding your breath for as long as is comfortable.

8. If you are to take further puffs keep the inhaler upright and wait about half a minute before repeating steps 2 to 6.

9. Replace the mouthpiece cover by firmly pushing and snapping the cap into position.

<u>IMPORTANT:-</u>

Do not rush Stages 5, 6 and 7. It is important that you start to breathe in as slowly as possible just before operating your Inhaler.

Practise in front of a mirror for the first few times. If you see 'mist' coming from the top of the inhaler or the sides of your mouth you should start again from stage 2.

APPENDIX E: CONSORT CHECKLIST

SMART study CONSORT 2010 checklist of information

Section/Topic	Item No	Checklist item	Reported in Chapter
Title and abstract			
	1a	Identification as a randomised trial in the title	Yes
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	1
	2b	Specific objectives or hypotheses	1
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	None
Sample size	7a	How sample size was determined	4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	4
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	4
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	6
	13b	For each group, losses and exclusions after randomisation, together with reasons	6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	Completed
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	6
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	6
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	6
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	6
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	6 and Appendix H: adverse events
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	7
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	7
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	7
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	Appendix A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	4

APPENDIX F: ETHICS APPROVAL

Health and Disability Ethics Committees

Multi-region Ethics Committee
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington 6145
Phone (04) 470 0655
(04) 470 0646
Fax (04) 496 2340
Email: multiregion_ethicscommittee@moh.govt.nz

12 May 2010

Professor Richard Beasley
Medical Research Institute of New Zealand
3rd Floor, 99 The Terrace
PO Box 10055
Wellington

CC: Dr Tanya Baker
Medical Research Institute of New Zealand
3rd Floor
99 The Terrace
PO Box 10055
Wellington

Dear Richard

Ethics ref: **MEC/09/11/127**
Study title: A randomised, controlled trial to investigate the "real-life" use of the Symbicort® "SMART" regime in adult asthma. Protocol No. SM01

Thank you for your letter dated the 19th of April 2010 informing the Multi-region Ethics Committee of changes that have been made to the study Protocol. The updated documentation has been reviewed and approved by the Chairperson of the Multi-region Ethics Committee under delegated authority.

Approved documents:

1. **Protocol No SM01, version 2 dated 19 April 2010**
2. Participant Information Sheet, version 2, dated 12 April 2010 (final and tracked changes versions)
3. Participant Informed Consent Form, version 2, dated 12 April 2010 (final and tracked changes versions)
4. SMART appointment card, version 2, dated 12 April 2010
5. Standard appointment card, version 2, dated 12 April 2010
6. SMART (symptoms) asthma self management plan (Plan 1), version 1, dated 12 April 2010
7. SMART (Peak flow) asthma self management plan (Plan 2), version 1, dated 12 April 2010
8. Standard (symptoms) asthma self management plan (Plan 3), version 1, dated 12 April 2010
9. Standard (Peak flow) asthma self management plan (Plan 4), version 1, dated 12 April 2010
10. Care of Inhaler advice sheet, version 1, dated 12 April 2010
11. Letter from health provider to patient, version 1, dated 12 April 2010
12. Letter to patient from MRINZ, version1, dated 12 April 2010
13. SMART study radio advertisement, version 1, dated 12 April 2010
14. A4 Poster with tear-offs, version 1, dated 9 April 2010

15. A3 Poster with tear-offs, version 1, dated 9 April 2010
16. A5 SMART flyer, version 1, dated 9 April 2010
17. MRINZ webpage Ad, version 1, dated 9 April 2010
18. SMART Newspaper Ad, version 1, dated 9 April 2010
19. Satisfaction with Inhaled Asthma treatment questionnaire, copyright AstraZeneca R&D Lund, Sweden

In addition, the following documents were reviewed and noted by the Chairperson of the Multi-region Ethics Committee under delegated authority.

Noted documents:

1. Locality Assessments and Part 4 Declaration for Dr Andrew Corin of Tauranga.
2. Hutt Valley DHB Locality Assessment (please note that patients will not be seen at Hutt Hospital but this site is providing patient referrals only).

Please do not hesitate to contact me should you have any queries.

Yours sincerely

Claire Lindsay
Administrator
Multi-region

APPENDIX G: CLINICAL TRIAL REGISTRATION DOCUMENT

ANZCTR
Australian New Zealand Clinical Trials Registry

Australian New Zealand Clinical Trials Registry

Trial Details

indicate updates made to monitored data item(s) since trial registration. These data item(s) are monitored to ensure they comply with the WHO / journal editors standards.

View Trial at Registration | View current trial information

History of Trial details

Request Number:	335093
ACTR Number:	ACTRN12610000515099
Trial Status:	Registered
Date Submitted:	9/06/2010
Date Registered:	22/06/2010
Date Last Updated:	02/03/2012
Registration Type:	Prospective registered

Page 1

Public title:	A study to investigate the "real-life" use of the Vannair "SMART" regime in adult asthma (the SMART study).
ANZCTR registration title:	A randomised, controlled trial to investigate the "real-life" use of the Vannair "SMART" regime in adult asthma (the SMART study)
Secondary ID:	Nil
UTN:	
Trial acronym:	

Page 2

Health condition(s) or problem(s) studied:	
Asthma	
Condition category:	**Condition code:**
Respiratory	Asthma

Page 3

Description of intervention(s) / exposure:	The intervention is inhaled budesonide/eformoterol (Vannair (Registered Trademark) 200/6 micrograms) two actuations taken twice daily and as required for asthma symptom relief as per the "SMART" (Single combination inhaler as Maintenance And Reliever Therapy) regime. The duration of the intervention is 24 weeks. There is no subsequent follow-up period planned.
Intervention code:	Treatment: drugs
Comparator / control treatment:	The control is inhaled budesonide/eformoterol (Vannair (Registered Trademark) 200/6 micrograms) two actuations taken twice daily along with a salbutamol inhaler (Ventolin (Registered Trademark) 100 micrograms) taken as required for asthma symptom relief (the "Standard" treatment regime). The duration of the control treatment is 24 weeks. There is no subsequent follow-up period planned.
Control group:	Active

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Primary outcome:	The proportion of high beta-agonist use episodes in the SMART group compared with the Standard Group as defined by the proportion of patients in the SMART group who at any point within the 24 week study period used greater than 8 actuations of Vannair as a reliever per 24 hour period compared to the proportion of patients in the Standard group who used greater than 16 actuations of Ventolin in a 24 hour period, as recorded by the electronic monitoring devices.
Timepoint:	As assessed after the 24 week study period on the data from the electronic monitoring devices.
Secondary outcome 1:	Asthma Control Questionnaire (ACQ) Score
Timepoint:	As assessed after 24 weeks of treatment and compared with the baseline score.
Secondary outcome 2:	The proportion of patients in the SMART group who markedly overuse Vannair as a reliever (defined as greater than 12 and 16 reliever actuations per 24 hour period) compared with Standard group patients who markedly overuse salbutamol as a reliever (defined as greater than 24 and 32 Ventolin actuations per 24 hour period respectively), as recorded by the electronic monitoring devices.
Timepoint:	As assessed after the 24 week study period on the data from the electronic monitoring devices.
Secondary outcome 3:	The proportion of patients who underuse their maintenance Vannair treatment in the SMART versus Standard groups, defined as 0 or 1 inhalations within a 24 hour period, as recorded by the electronic monitoring devices.
Timepoint:	As assessed after the 24 week study period on the data from the electronic monitoring devices.
Secondary outcome 4:	Patterns of use of reliever Vannair and salbutamol around the time of exacerbations. Exacerbation data will be recorded from patients at study visits and patterns of use of reliever medication will be obtained from the electronic monitoring devices.
Timepoint:	As assessed from data collected at the time of study visits over the 24 weeks of treatment.

Secondary outcome 5:	Number of severe exacerbations in the SMART versus Standard groups. Exacerbation data will be recorded from patients at study visits.
Timepoint:	As assessed from data collected at the time of study visits over the 24 weeks of treatment.

Page 5

Key inclusion criteria:	1. A doctor's diagnosis of asthma; 2. A current prescription for inhaled corticosteroid (ICS) medications; 3. No change in the dose of ICS in the last month; 4. An asthma exacerbation in the previous year where the patient presented to a General Practitioner or Emergency Department and was prescribed a course of oral steroids and/or received a spacer/nebuliser-delivered bronchodilator and patients who self-administered prednisone for asthma for at least 3 days.
	1. A doctor's diagnosis of asthma; 2. A current prescription for inhaled corticosteroid (ICS) medications; 3. No change in the dose of ICS in the last month; 4. An asthma exacerbation in the previous year where the patient presented to a General Practitioner or Emergency Department and was prescribed a course of oral steroids and/or received a spacer/nebuliser-delivered bronchodilator. TO 1. A doctor's diagnosis of asthma; 2. A current prescription for inhaled corticosteroid (ICS) medications; 3. No change in the dose of ICS in the last month; 4. An asthma exacerbation in the previous year where the patient presented to a General Practitioner or Emergency Department and was prescribed a course of oral steroids and/or received a spacer/nebuliser-delivered bronchodilator and patients who self-administered prednisone for asthma for at least 3 days. Reason: A proportion of severe asthmatics will have been prescribed prednisone by their physician or GP for self-administration at home in the event of an exacerbation, as per their self-management plan. Prednisone use for at least 3 days fulfils the definition of a severe asthma exacerbation used by the European Respiratory Society and so we have updated the wording of this inclusion criterion in order to allow eligibility to the study for these patients. Updated on 19/10/2010 9:18:57 AM
Minimum Age:	16 Years
Maximum Age:	65 Years
Gender:	Both males and females
Healthy volunteers?	No
Key exclusion criteria:	1. Onset of respiratory symptoms after the age of 40 years in current or ex-smokers with a greater than or equal to 10 pack years smoking history; 2. use of an at-home nebuliser (unless patients agree to withhold nebuliser use for the study duration); 3. treatment with oral prednisone in the previous 4 weeks; 4. diagnosis of Chronic Obstructive Pulmonary Disease (COPD), interstitial lung disease or bronchiectasis; 5. unsuitable cardiovascular or other medical history, or any other safety concern at the investigator's discretion; 6. unable or unwillling to give consent to participate, to follow the study requirements and/or to change from current asthma treatment regime.
	1. Onset of respiratory symptoms after the age of 40 years in current or ex-smokers with a greater than or equal to 10 pack years smoking history; 2. use of an at-home nebuliser (unless patients agree to withhold nebuliser use for the study duration); 3.

	previous admission to an Intensive Care Unit with life-threatening asthma; 4. treatment with oral prednisone in the previous 4 weeks; 5. diagnosis of Chronic Obstructive Pulmonary Disease (COPD), interstitial lung disease or bronchiectasis; 6. unsuitable cardiovascular or other medical history, or any other safety concern at the investigator's discretion; 7. unable or unwillling to give consent to participate, to follow the study requirements and/or to change from current asthma treatment regime. TO 1. Onset of respiratory symptoms after the age of 40 years in current or ex-smokers with a greater than or equal to 10 pack years smoking history; 2. use of an at-home nebuliser (unless patients agree to withhold nebuliser use for the study duration); 3. treatment with oral prednisone in the previous 4 weeks; 4. diagnosis of Chronic Obstructive Pulmonary Disease (COPD), interstitial lung disease or bronchiectasis; 5. unsuitable cardiovascular or other medical history, or any other safety concern at the investigator's discretion; 6. unable or unwillling to give consent to participate, to follow the study requirements and/or to change from current asthma treatment regime. Reason: Patients with asthma who use a home nebuliser may be eligible to enter the study if they agree to withhold nebuliser use for the study duration, as discussed with the patient by the Investigator at Visit 1. Updated on 6/12/2010 4:34:35 PM
	1. Onset of respiratory symptoms after the age of 40 years in current or ex-smokers with a greater than or equal to 10 pack years smoking history; 2. use of an at-home nebuliser; 3. previous admission to an Intensive Care Unit with life-threatening asthma; 4. treatment with oral prednisone in the previous 4 weeks; 5. diagnosis of Chronic Obstructive Pulmonary Disease (COPD), interstitial lung disease or bronchiectasis; 6. unsuitable cardiovascular or other medical history, or any other safety concern at the investigator's discretion; 7. unable or unwillling to give consent to participate, to follow the study requirements and/or to change from current asthma treatment regime. TO 1. Onset of respiratory symptoms after the age of 40 years in current or ex-smokers with a greater than or equal to 10 pack years smoking history; 2. use of an at-home nebuliser (unless patients agree to withhold nebuliser use for the study duration); 3. previous admission to an Intensive Care Unit with life-threatening asthma; 4. treatment with oral prednisone in the previous 4 weeks; 5. diagnosis of Chronic Obstructive Pulmonary Disease (COPD), interstitial lung disease or bronchiectasis; 6. unsuitable cardiovascular or other medical history, or any other safety concern at the investigator's discretion; 7. unable or unwillling to give consent to participate, to follow the study requirements and/or to change from current asthma treatment regime. Reason: Prior Intensive Care Unit (ICU) admission removed as an exclusion criterion: As the study is aiming to study the potential benefits of the SMART regime specifically in severe asthmatics, patients who have had prior ICU admissions for asthma form part of the target group for this study. The removal of prior ICU admission as an exclusion criterion will therefore allow a representative group of severe asthmatics to be eligible for this study. Updated on 19/10/2010 9:18:56 AM

Study type:	Interventional
Purpose of the study:	Treatment
Allocation to intervention:	Randomised controlled trial

Describe the procedure for enrolling a subject and allocating the treatment (allocation concealment procedures):	Investigators will screen patients for eligibility for entry into the study at Visit 1. If found eligible, allocation concealment will occur by means of sealed opaque envelope, containing details of allocation to the SMART or Standard study group.
Describe the methods used to generate the sequence in which subjects will be randomised (sequence generation):	Randomisation will be performed in blocks.
Masking / blinding:	Open (masking not used)
Assignment:	Parallel
Other design features (specify):	
Type of endpoint(s):	Safety/efficacy

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Phase	Phase 4
Anticipated or actual date of first participant enrolement:	29/06/2010
Target sample size:	300
Recruitment status:	Closed: follow-up complete

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Funding source:	Government funding body e.g. Australian Research Council
Name:	Health Research Council of New Zealand
Address:	PO Box 5541, Wellesley Street, Auckland 1141

Country:	New Zealand
Primary sponsor:	Charities/Societies/Foundations
Name:	Medical Research Institute of New Zealand
Address:	Private Bag 7902 Wellington 6242
Country:	New Zealand
Secondary sponsor:	None
Name:	
Address:	
Country:	
Other collaborator:	

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Has the study received approval from at least one ethics committee?	Yes
Ethics Committee name:	Multi Region Ethics Committee
Address:	Ministry of Health Level 2, 1-3 The Terrace PO Box 5013 Wellington 6145
Country:	New Zealand
Date of approval:	12/05/2010
HREC Number:	MEC/09/11/127
Countries of recruitment:	Outside Australia
	New Zealand
Brief summary:	The recommended treatment for preventing asthma exacerbations in adults with moderate-severe asthma is regular inhaled corticosteroids (ICS) combined with an inhaled long-acting beta-agonist drug (LABA). This therapy is commonly prescribed as a fixed combination inhaler, such as Seretide (Registered Trademark), Symbicort (Registered Trademark) or Vannair (Registered Trademark) and is taken twice daily

	with a short-acting beta-agonist (SABA) used as rescue therapy in the event of an exacerbation ("STANDARD" regime). An alternative regime in which patients take their Vannair (Registered Trademark) combination inhaler both as Maintenance And Reliever Therapy (referred to as SMART) has recently been proposed. A large clinical trial programme has shown that Symbicort (Registered Trademark) (budesonide/eformoterol) taken according to the SMART regime is more effective than the STANDARD regime. However, these studies were undertaken under strict clinical trial conditions in highly selected populations. Additionally it is not clear how the use of budesonide/eformoterol given according to the SMART regime improves outcomes, or whether its use by patients in the situation of worsening asthma or severe exacerbations is associated with significant risk. This study aims to assess the effect on asthma control of budesonide/eformoterol given using the SMART regime in a population of high-risk asthmatics in real life and to measure (using electronic monitoring devices) the actual use of budesonide/eformoterol when used according to the SMART regime.
Trial website:	
Presentations / publication list:	

Contact person for public queries

Name:	Dr Mitesh Patel
Address:	Medical Research Institute of New Zealand Private Bag 7902 Wellington 6242
Country:	New Zealand
Tel:	+64 4 805 0235
Fax:	+64 4 389 5707
Email:	mitesh.patel@mrinz.ac.nz

Contact person for scientific queries

Name:	Dr Mitesh Patel
Address:	Medical Research Institute of New Zealand Private Bag 7902 Wellington 6242
Country:	New Zealand
Tel:	+64 4 805 0235
Fax:	+64 4 389 5707
Email:	mitesh.patel@mrinz.ac.nz

APPENDIX H: ADVERSE EVENTS IN THE SMART STUDY RCT

All adverse events occurring in the study are reported below.

	SMART (n=151)		Standard (n=152)	
Adverse event	**Number of participants**	**%**	**Number of participants**	**%**
Upper respiratory tract infection	66	43·7	65	42·8
Injury/trauma/musculoskeletal ailment	27	17·9	17	11·2
Adverse taste	19	12·6	19	12·5
Voice change (including hoarseness)	15	9·9	6	3·9
Lower respiratory tract infection/ pneumonia/chest infection/bronchitis	12	7·9	15	9·9
Throat or mouth irritation	10	6·6	6	3·9
Tremor	8	5·3	5	3·3
Sinusitis	8	5·3	9	5·9
Headache	7	4·6	8	5·3
Dry mouth or throat	7	4·6	9	5·9
Palpitations	6	4·0	5	3·3
Conjunctivitis or eye infection	6	4·0	1	0·7
Thrush (oral or genital)	5	3·3	5	3·3
Sleep disturbance or insomnia	5	3·3	0	0·0
Ear infection	4	2·6	4	2·6
Gynaecology ailment	4	2·6	0	0·0

Muscle cramp	3	2·0	6	3·9
Migraine	3	2·0	3	2·0
Hayfever or allergic rhinitis	3	2·0	8	5·3
Gastrointestinal illness	3	2·0	3	2·0
Cough	2	1·3	4	2·6
Weight gain	2	1·3	0	0·0
Skin rash	2	1·3	6	3·9
Miscarriage	2	1·3	1	0·7
Mouth ulcers	2	1·3	1	0·7
Urinary tract infection	2	1·3	3	2·0
Indigestion or reflux	2	1·3	1	0·7
Diarrhoea and/or vomiting	2	1·3	7	4·6
Tachycardia (self-limiting) *	1	0·7	0	0·0
Light headed	1	0·7	0	0·0
Nausea	1	0·7	5	3·3
Non cardiac chest pain (all self-limiting)	1	0·7	2	1·3
Restless	1	0·7	0	0·0
Pelvic infection	1	0·7	0	0·0
Skin bruising	1	0·7	0	0·0
Seizure	1	0·7	1	0·7
Pleurisy	1	0·7	0	0·0
Itch (pruritis)	1	0·7	0	0·0
Anxiety	1	0·7	0	0·0

Pre-existing mental health problem	1	0·7	1	0·7
Swelling of ankles	1	0·7	0	0·0
Dental problem	1	0·7	2	1·3
Sarcoid	0	0·0	1	0·7
Dizzyness	0	0·0	4	2·6
Tiredness	0	0·0	1	0·7
Weight loss	0	0·0	1	0·7
Diabetes	0	0·0	3	2·0
Mucous in throat	0	0·0	2	1·3
Food allergy	0	0·0	1	0·7
Skin cancer	0	0·0	1	0·7
Skin infection	0	0·0	1	0·7
Smoke inhalation	0	0·0	1	0·7
Cataract	0	0·0	2	1·3

*: documented by palpation by investigator; self-limiting