The importance of inhaler adherence in severe asthma and its relationship to clinical outcomes

AUTHOR(S)

Matshediso Mokoka

CITATION

Mokoka, Matshediso (2020): The importance of inhaler adherence in severe asthma and its relationship to clinical outcomes. Royal College of Surgeons in Ireland. Thesis. https://doi.org/10.25419/rcsi.13317500.v1

DOI

10.25419/rcsi.13317500.v1

The importance of inhaler adherence in severe asthma and its relationship to clinical outcomes

RCSI

Dr. Matshediso Mokoka MB BCh BAO MRCPUK MSc

Department of Respiratory Medicine

RCSI

A thesis submitted to the School of Postgraduate Studies, Faculty of Medicine and Health Sciences, Royal College of Surgeons in Ireland, in fulfilment of the Degree of Doctor of Medicine

Supervisors: Prof. Richard W Costello & Dr. John Faul

October 2018

Candidate Thesis Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a Degree of Doctor of Medicine, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere based on this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed: _____

Student Number: 15151425

Date: _____

IP Declaration

The contents of the enclosed manuscript are confidential and should not be disclosed, or disseminated in any way, to any third party other than to staff or students of the Royal College of Surgeons in Ireland or an external examiner appointed for reviewing the manuscript.

Table of contents

Contents

List of Abbreviations

ACT…… Asthma Control Test

ACQ…… Asthma Control Questionnaire

ATS…… American Thoracic Society

ANOVA…… Analysis of Variance

AQLQ…… Asthma Quality of Life Questionnaire

ATS…….. American Thoracic Society

AUC…… Area Under the Curve

BMI…… Body Mass Index

CD4……. Cluster of Differentiation 4

C.I…… Confidence Interval

COPD…….. Chronic Obstructive Pulmonary Disease

DPI……. Dry Powder Inhaler

ED……. Emergency Department

EDTA…….. Ethylene-diamine-tetraacetic acid

EQ-5D-3L……. European Quality of Life, 5 dimensions, 3 layers

ERS……. European Respiratory Society

FEV1…… Forced Expiratory Volume in 1 Second

FeNO…… Fractionated Exhaled Nitric Oxide

FVC…….... Forced Vital Capacity

GINA……. Global Initiative for Asthma

G-CSF……. Granulocyte Colony Stimulating factor

GP…… General Practitioner

INCA…….. Inhaler Compliance Assessment

ICS……. Inhaled Corticosteroids

IL…… Interleukins

IPS……. Inhaler Proficiency Score

ITT……. Intention To Treat

IQR…… Interquartile Range

LABA…… Long Acting Beta Agonist

LAMA……. Long Acting Muscarinic Antagonist

LQC…… Lower Quality Control

MCID…… Minimal Clinically Important Difference

MDI…… Metered Dose Inhaler

MI…… Multiple Imputation

ML…….. Millilitres

MPR……. Medication Possession Ratio

NSAIDs…… Non-Steroidal Anti-inflammatory Drugs

OCS……. Oral Corticosteroids

PEF…… Peak Expiratory Flow

PEFR……..Peak Expiratory Flow Rate

PIFR……. Peak Inspiratory Flow Rate

PP…….. Per protocol

QoL…… Quality of Life

RAST……..Radio-allergosorbent Test

RCP…….. Royal College of Physicians

RCTs……Randomized Control Trials

RV……. Residual Volume

SD……. Standard Deviation

TGF-beta…… Transforming Growth Factor-beta

TLR…….. Toll-like receptors

TLC……..Total Lung Capacity

TNF…….. Tumour Necrosis Factor

TSLP…….. Thymic Stromal Lymphopoietin

WPAI-Asthma…… Work Productivity and Activity Impairment – Asthma Questionnaire

WHO……. World Health Organization

List of Figures

List of Tables

List of Publications

1. **Inadequate assessment of adherence to maintenance medication leads to loss of power and increased costs in trials of severe asthma therapy. Results from a systematic literature review and modelling study. Matshediso C. Mokoka,** Melissa J. McDonnell, Elaine MacHale, Breda Cushen, Fiona Boland, Sarah Cormican, Christina Doherty, Frank Doyle, Richard W. Costello, Garrett Greene. European Respiratory Journal 2019; DOI: 10.1183/13993003.02161-2018

2. **In patients with severe uncontrolled asthma, does knowledge of adherence and inhaler technique using electronic monitoring improve clinical decision making? A protocol for a randomised controlled trial. Mokoka MC,** Lombard L, MacHale EM, Walsh J, Cushen B, Sulaiman I, Carthy DM, Boland F, Doyle F, Hunt E, Murphy DM, Faul J, Butler M, Hetherington K, Mark FitzGerald J, Boven JFV, Heaney LG, Reilly RB, Costello RW. BMJ Open. 2017 Jun 15;7(6): e015367. doi: 10.1136/bmjopen-2016-015367

3. **A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma**. Sulaiman I, Greene G, MacHale E, Seheult J, **Mokoka M**, D'Arcy S, Taylor T, Murphy DM, Hunt E, Lane SJ, Diette GB, FitzGerald JM, Boland F, Sartini Bhreathnach A, Cushen B, Reilly RB, Doyle F, Costello RW. Eur Respir J. 2018 Jan 4;51(1). pii: 1701126. doi: 10.1183/13993003.01126-2017. Print 2018 Jan. PMID:29301919

4. **Objective Assessment of Adherence to Inhalers by Patients with Chronic Obstructive Pulmonary Disease**. Sulaiman I, Cushen B, Greene G, Seheult J, Seow D, Rawat F, MacHale E, **Mokoka M**, Moran CN, Sartini Bhreathnach A, MacHale P, Tappuni S, Deering B, Jackson M, McCarthy H, Mellon L, Doyle F, Boland F, Reilly RB, Costello RW. Am J Respir Crit Care Med. 2017 May 15; 195(10):1333-1343. doi: 10.1164/rccm.201604-0733OC.

5. **The Impact of Common Inhaler Errors on Drug Delivery: Investigating Critical Errors with a Dry Powder Inhaler.** Sulaiman I, Seheult J, Sadasivuni N, MacHale E, Killane I, Giannoutsos S, Cushen B, **Mokoka MC,** Sartini Bhreathnach A, Boland F, Reilly RB, Costello RW. J Aerosol Med Pulm Drug Deliv. 2017 Mar 9. doi: 10.1089/jamp.2016.1334

6. **A Method to Calculate Adherence to Inhaled Therapy that Reflects the Changes in Clinical Features of Asthma**. Sulaiman I, Seheult J, MacHale E, Boland F, O'Dwyer SM, Rapcan V, D'Arcy S, Cushen B, **Mokoka M**, Killane I, Ryder SA, Reilly RB, Costello RW. Ann Am Thorac Soc. 2016 Nov;13(11):1894-1903

Poster Presentations (First Author):

1. **Inhaled Corticosteroids (ICS) and Long Acting Beta-adrenoceptor Agonist (LABA) Therapy Adherence repoting and Monitoring in clinical trials of severe adult drug treatments: A systematic review Trials. Mokoka MC,** Green G, Mc Donnell MJ, Boland F, Cormican S, Doyle F, Costello RW. American Thoracic Society (pp A1402-A1402)

2. **Adherence to Inhaled Corticosteroids and Long Acting Beta-adrenoceptor Agonist Therapy in Severe Asthma Clinical Trials. Mokoka MC,** Mc Donnell MJ, Cormican S, Boland F, Doyle F, Costello RW. Thorax December Issue 2016

Abstract

Patients with asthma who remain troubled with symptoms and asthma attacks despite the use of long acting beta-agonist and inhaled corticosteroid therapy are classed as having severe asthma. Some of these patients have "'difficult to control'" asthma because of poor adherence or inhaler technique, while others have asthma that is 'refractory' to treatment. Identifying and addressing poor adherence to ICS/LABA therapy is essential in management of patients with severe asthma. In clinical trials, adherence assessment ensures that only patients with 'refractory' asthma are enrolled and reduces the variance in the results that could result as a consequence of not assessing adherence. In clinical practice assessing and addressing adherence allows appropriate use of biologic therapy.

The aim of this thesis was to develop ways to assess adherence to maintenance asthma therapy. Firstly, I conducted a systematic review, investigating whether, and how adherence to inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) is assessed in the screening and run-in phase of randomised controlled trials of 'add on therapy' in severe asthma. I found that adherence to ICS/LABA therapy assessment and reporting is rarely done and that the methods used to assess adherence in the randomised controlled trials were inadequate. To overcome these inadequacies, I conducted a randomised clinical trial to assess adherence in patients with severe asthma using the INhaler Compliance Assessment (INCA) device, a digital audio recording device that provides information on inhaler time of use and inhaler technique. I devised pathways that incorporated this information, as well as patient's symptom scores and peak expiratory flow to design a physician script tailored to optimise asthma treatment. The study assessed the value of using an objective method of assessing inhaler adherence in tailored education therapy and how it guides clinicians to make informed clinical decisions in treating patients with severe asthma.

Acknowledgments

Firstly, I would like to thank Professor Richard W. Costello who has provided me with this research opportunity. I would like to thank him for his continued counsel and guidance he has provided me to help me complete this thesis.

I would also like to thank Dr Frank Doyle and Dr John Faul for their support and constructive criticism of my research for the past two and a half years.

I would like to thank all my colleagues; Ms Lorna Lombard, Ms Joanne Walsh, Ms Chloe Carpenter, Mr Shane Bergin, and Ms Lorraine Thompson and for their support and for helping with data collection. Thanks also to Dr Melissa Mc Donnell, Dr Fiona Boland and Dr Garrett Greene for their statistics support and friendship. I would also like to thank Ms Elaine MacHale for her support.

I would also like to thank my collaborators Prof. Liam Heaney, Dr Job van Boven and Prof. Mark J FitzGerald.

Dedication

This thesis is dedicated to David and Cora who have constantly supported my career. I am grateful and humbled by their constant encouragement, patience, unconditional love and unwavering faith which enabled me to complete this thesis.

I would also like to dedicate this to my parents' in-law Francis and Mary and my siblings who have always supported me unconditionally and kept me in their prayers.

Chapter 1. Introduction

1.1 STATEMENT OF THESIS SUBJECT

In this chapter, first I will describe the assessment of patients with severe uncontrolled asthma. This will include defining asthma control and discussing how to assess asthma control. I will also evaluate the literature on defining severe asthma and assessing asthma severity. I will then proceed to describe inhaler adherence and how to distinguish patients with "difficult to treat" asthma from those with "'refractory' asthma." Finally, I will discuss the impact of adherence on clinical outcomes in asthma and how poor adherence and inhaler technique can be assessed.

1.2 EVALUATION OF PATIENTS WITH SEVERE ASTHMA

Asthma is a heterogeneous chronic inflammatory disease of the airways, with notable phenotypes and endo-types. Inhaled corticosteroid therapy has been the mainstay treatment because of the anti-inflammatory properties (1). Despite management with guideline-driven standard of care therapy, a significant proportion (10-40%) of patients remains uncontrolled (2). Patients who continue to have uncontrolled symptoms and frequent exacerbations, despite treatment with medium or high dose, inhaled corticosteroids may be classified as having severe asthma. Persistent symptoms, frequent exacerbations and medication side effects have profound consequences for mental and emotional health, relationships, and careers in patients with severe asthma (3). To achieve a comprehensive asthma management strategy, it is critical to confirm asthma diagnosis, treat comorbidities as well as assess and address adherence to inhaled therapy (4).

1.2.1 Confirming asthma diagnosis

In every patient who continues to have persistent symptoms or frequent exacerbations despite high-intensity treatment, it is essential first to confirm the diagnosis of asthma. About 25-35% of patients diagnosed with asthma in primary

care have been found not to have objective diagnostic evidence that they have the condition (5). Hence, to establish a true diagnosis of asthma objective evidence of disordered airway physiology must be confirmed. Available tests that may demonstrate variable airflow limitation, the characteristic physiological feature of asthma, include daily peak expiratory flow measurements; reversibility tests with a bronchodilator drug; and challenge tests with a bronchoconstriction agent.

A diagnosis of asthma will be established if there is an improvement or reduction in forced expiratory volume in one second (FEV1) of ≥12% and >200 millilitres (mL) from baseline. It is worth noting that because patients will be on controller treatment, the FEV1 may be within the normal predicted range. In such cases variable expiratory airflow limitation can be detected with home monitoring of peak flow. In a patient on maintenance ICS, diurnal variability in peak expiratory flow (PEF) of >10% in adults can be used to confirm a diagnosis of asthma. The diurnal variability in PEF is calculated as the average of daily amplitude per cent mean {((Day's highest – day's lowest)/mean of day's highest and lowest) x 100}over 1–2 weeks (4). FEV1 is more reliable than the PEF and if PEF is used to confirm variable expiratory airflow limitation the same PEF meter should be used because variations of about 20% in PEF measurements have been shown in different meters (6). In patients with variable symptoms in the absence of variable airflow limitation, bronchial provocation tests should be considered if the FEV1 is >70%. Patients should be considered for step-down therapy if they have few respiratory symptoms, the lung function is normal and there is no evidence of variable expiratory airflow limitation (4). The repeated failure to demonstrate variable airflow or obstruction over time, as well as the absence of symptoms after stepping down treatment time, would suggest that the diagnosis of asthma is unlikely. The above indicates that there are several ways to diagnose asthma and, hence, in patients with severe uncontrolled asthma, the first crucial step is to definitively establish a diagnosis of asthma.

1.2.2 Symptom control assessment

In those patients who have a confirmed diagnosis of asthma but don't seem to respond to asthma maintenance treatment, asthma control should be assessed. Global Initiative for Asthma (GINA) guidelines describe the goals of asthma treatment as a combination of control of patients' symptoms as well as the prevention of future adverse outcomes, which include exacerbations, a rapid decline in lung function and side-effects of treatment (4). Therefore, the assessment of asthma control must include both assessment of symptoms and the risk of future adverse asthma outcomes such as exacerbations, fixed airflow limitation and medication side-effects.

1.2.2.1 *Asthma controlassessment*

The interaction between the patient's genetic background, the underlying asthma pathophysiology, the environment, the asthma treatment and psychosocial factors play a significant role in asthma control. Asthma symptoms are subjective and vary in frequency and intensity. Therefore, validated numerical and categorical symptom control tools have been developed to assess patients' symptoms. Numerical asthma control tools are advantageous because they are more sensitive to change in symptom control than categorical tools (7). Numerical symptom screening tools include the asthma control test (ACT) and asthma control questionnaire (ACQ), while categorical symptom control tools include the consensus-based Royal College of Physicians (RCP) tool. The RCP symptom control assessment test is a three questions tool (8), which assesses difficulty sleeping, daytime symptoms and activity limitation due to asthma in the previous month. The ACQ was generated from a list of all symptoms used to assess control by expert asthma clinicians (9). The clinicians scored each symptom for its importance in evaluating asthma control and the five highest scoring symptoms were selected for the ACQ. The questionnaire was shown to be responsive to change in asthma control compared to asthma diary in a 9-week observational study of 50 adults with symptomatic asthma (10).

The ACT questionnaire was developed by a group composed of primary care clinicians and asthma specialists and comprises 5 items assessing asthma symptoms (daytime and nocturnal), use of rescue medications and the effect of asthma on daily functioning (11). 471 recruited participants were asked to complete the survey during a routine, previously scheduled physician office visit and responses for each of the 5 items are added to yield a score ranging from 5 (poor control of asthma) to 25 (complete control of asthma). The ACT has been validated and it accurately assesses asthma control compared with specialist ratings on the basis of history, physical examination, and lung function tests and with the previously validated (12).These validated symptoms assessment scores help in clarifying that the symptoms are due to asthma as well as assessing patient's progress.

1.2.2.2 *Assessing the risk of future exacerbations*

An asthma exacerbation has been defined as "a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome" (13). In addition to poor asthma control, there are additional independent factors have been shown to contribute to increasing the risk of future asthma exacerbations. These include a history of one exacerbation or more in the previous year, poor adherence to asthma treatment, incorrect inhaler technique, chronic sinusitis and smoking (14).

Most acute exacerbations are caused by viral respiratory tract infections (15) and, hence, treatment with inhaled short-acting beta2-agonists (SABAs), systemic corticosteroid treatment (either oral or intravenous), and ipratropium bromide, and, in some cases, magnesium sulphate with supplementary oxygen for patients who are hypoxemic is recommended in those with severe exacerbations (16). There has been conflicting evidence with regards to whether bacteria cause acute exacerbations (15) and therefore, antibiotics are recommended if there are clear signs, symptoms or laboratory evidence of bacterial infection (16).

1.2.3 Assessing fixed airflow limitation

Identification of future risk for adverse asthma outcomes, such as fixed airflow limitation and side-effects of medications is an essential part of assessing asthma control. Patients' with frequent exacerbations experience accelerated decline in FEV1 (17). An annual decline in FEV1 of about 30.2mls has been associated with an asthma exacerbation requiring hospitalisation (17). Frequent exacerbations cause accelerated structural changes and remodelling of the airways. Consequently, fixed airway obstruction ensues. Low baseline lung function, FEV1 <60% predicted, has also been associated with increased risk of exacerbations (18-21). Additionally, exposure to cigarette smoke or noxious agents, chronic mucus hypersecretion, and asthma exacerbations in patients not taking ICS have been associated with an increased risk of developing fixed airflow limitation (22). Therefore, lung function must be assessed at diagnosis, and after three to six months of commencing controller treatment to determine the patient's personal best FEV1 and to monitor clinical course (23).

1.2.4 Defining severe asthma

After confirming the diagnosis of asthma and reviewing ICS/LABA treatment, monitoring of treatment response is essential because there is a proportion of patients who continue to have uncontrolled symptoms and frequent exacerbations, despite treatment with medium or high dose inhaled corticosteroids. These patients may be classified as having severe asthma. The concept of "asthma severity" has evolved substantially over the years (Table 1-1). Defining asthma severity is complicated by the widespread use of the word severity to refer to the intensity of individual features, such as severity of airway obstruction, or the severity of an exacerbation. Furthermore, a clinician's definition of severe asthma may vary from the patient's perception of asthma severity because the patient's focus will be on the intensity of day to day symptoms or how asthma affects their quality of life (24).

In the 1995 GINA guidelines, overall asthma severity was assessed primarily based on the patient's clinical characteristics before commencing treatment (25). Before initiating therapy, asthma severity was categorised into intermittent, mild persistent, moderate persistent and severe persistent, based on symptoms, reliever use, night waking and lung function (either PEF or the FEV1 per cent predicted). Choosing patient's asthma initial treatment was determined by the classification of asthma being intermittent, mild persistent moderate or severe persistent (25). A similar classification was published in 1999 by the National Asthma Education and Prevention Program guidelines (26) and, later by the 2002 GINA guidelines in 2002. These guidelines published a severity of asthma classification that was categorised by the patient's pre-treatment clinical characteristics.

In 2007 a WHO definition of severe asthma was proposed by a group of experts, describing severe asthma by the level of current clinical control and risks. Severe asthma was defined as uncontrolled asthma which can result in the risk of frequent severe exacerbations (or death) and adverse reactions to medications or chronic morbidity (including impaired lung function or reduced lung growth in children) (27). Severe asthma was further categorised into three groups: untreated severe asthma; difficult-to-treat severe asthma; and treatment-resistant severe asthma. If patients had persistent symptoms and frequent exacerbations because of unavailable therapy or undiagnosed asthma, this was classified as untreated severe asthma. Patients with poor adherence or existing co-morbidity or exposure to environmental triggers as well as the inappropriate or incorrect use of medicines were identified as having difficult to treat asthma. Treatment-resistant severe asthma was diagnosed if asthma control was not achieved despite the highest level of recommended treatment or if asthma control required the use of the highest level of prescribed medication (28).

Subsequently, different asthma expert working groups published criteria for defining severe asthma that incorporates the use of high-dose anti-inflammatory

treatment (Table 1-1). A definition of severe asthma incorporating an occurrence of one or more exacerbations in the past year despite oral corticosteroids or high-dose ICS has been described previously (29). The American Thoracic Society (ATS) Workshop defined severe asthma as being present in those "patients with persistent symptoms, asthma exacerbations or airway obstruction despite high medication use, in addition to those who require high medication doses to maintain good disease control" (30). Dolan et al. (31) described severe asthma as asthma that includes patients with high use of the healthcare system or high medication use in the previous year. These different criteria include both patients who experience frequent exacerbations despite high doses of ICS/LABA treatment and patients who require high doses of ICS/LABA treatment to maintain good asthma control. Defining frequent exacerbations, despite high doses of ICS/LABA, is only accurate if patients are adherent to the prescribed therapy. Therefore, it is crucial to assess and address non-adherence to ensure appropriate prescription of high dose ICS/LABA treatment. Similarly, factors that trigger asthma attacks and co-morbidities should be evaluated and treated. Addressing non-adherence and managing persistent comorbidities enables a clear distinction between difficult to treat asthma and 'refractory' asthma. Uncontrolled asthma that is due to factors such as persistent environmental exposures aggravating comorbidities, poor adherence and inadequate inhaler technique suggest 'difficult to treat asthma' (32). Therefore, a diagnosis of severe asthma should be reserved for patients with 'refractory' asthma; those in whom treatment of comorbidities is complete and non-adherence to controller medication has been assessed and addressed (33).

Table 1-1 The progression of definitions of severe asthma over time

PEFR: peak expiratory flow rate; FEV1: forced expiratory volume in 1 second; ATS: American thoracic society; ERS: European thoracic society

Progression /change in consensus statements in defining severe asthma		
Consensus statement and year	**Categorisation of severe asthma**	**Description**
1995 GINA guidelines	Categorised by the patient's pre-treatment clinical characteristics.	Mild persistent, moderate persistent and severe persistent, based on symptoms, reliever use, night waking and lung function (either PEF or the FEV1 per cent predicted).
1999 National Asthma Education and Prevention Program guidelines	Categorised by the patient's pre-treatment clinical characteristics.	Mild persistent, moderate persistent and severe persistent
1999 ERS guidelines	Difficult asthma and uncontrolled asthma	Difficult asthma was defined as asthma remaining uncontrolled despite high-dose ICS with or without systemic gluco-corticosteroids. Uncontrolled asthma was defined as persistent asthma symptoms or recurrent exacerbations

Progression /change in consensus statements in defining severe asthma		
Consensus statement and year	**Categorisation of severe asthma**	**Description**
Proceedings of the ATS Workshop on 'refractory' Asthma 2002	Introduction of the term 'refractory' asthma. Eligibility for severe 'refractory' asthma required at least one major and two minor criteria.	The definition of severe asthma included two included one of two major criteria (daily use of high-dose inhaled corticosteroids and/or use of systemic corticosteroids) and at least two of the seven minor criteria (symptoms; frequent, severe, or life-threatening exacerbations; lung function; controller use; and loss of control when corticosteroids were tapered).
2002 GINA guidelines	Patient's pre-treatment clinical characteristics such as airflow limitation/variability were used to categorise the severity of the asthma into four steps: intermittent, mild persistent, moderate persistent and severe persistent.	Intermittent asthma was described as: symptoms occurring less than once a week; brief exacerbations; nocturnal symptoms <2 per month; FEV1 or PEF ≥ 80% predicted and PEF or FEV1 variability < 20%.

Progression /change in consensus statements in defining severe asthma		
Consensus statement and year	**Categorisation of severe asthma**	**Description**
		Mild persistent asthma was described as: symptoms occurring more than once a week but less than once a day; exacerbations may affect activity and sleep; nocturnal symptoms occurring more than twice a month; FEV1 or PEF ≥ 80% predicted; PEF or FEV1 variability 20-30% . Moderate persistent asthma was described as: symptoms occurring daily; exacerbations may affect activity and sleep; nocturnal symptoms occurring more than once a week; daily use of inhaled short-acting beta-2-agonist (SABA); FEV1 or PEF 60-80% predicted; PEF or FEV1 variability > 30%

Progression /change in consensus statements in defining severe asthma		
Consensus statement and year	**Categorisation of severe asthma**	**Description**
		Severe persistent was described as: symptoms occurring daily; frequent exacerbations; frequent nocturnal asthma symptoms; limitation of physical activities; FEV1 or PEF ≤ 60% predicted; PEF or FEV1 variability > 30%
2007 World Health Organization	Severe asthma described by the level of current clinical control and risks. Categorised into three groups: untreated severe asthma; difficult-to-treat severe asthma and treatment-resistant severe asthma.	Uncontrolled asthma which can result in the risk of frequent severe exacerbations (or death) and adverse reactions to medications or chronic morbidity (including impaired lung function or reduced lung growth in children)
2010 World Health Organization Consultation on Severe Asthma	Severe asthma categorised into three groups: (1) untreated severe asthma, (2) difficult-to-treat severe asthma, and (3) treatment-resistant severe asthma. Treatment-resistant asthma was further	Asthma control description included the responsiveness to treatment and future risk. Severe asthma was defined as uncontrolled asthma which can result in the risk of frequent severe exacerbations (or death) and

Progression /change in consensus statements in defining severe asthma		
Consensus statement and year	**Categorisation of severe asthma**	**Description**
	defined as uncontrolled asthma despite the highest level of recommended treatment and asthma for which control can be maintained only with the highest level of recommended treatment.	adverse reactions to medications or chronic morbidity (including impaired lung function or reduced lung growth in children)
Innovative Medicines Initiative, 2011	Poorly controlled asthma	Algorithm to distinguish difficult-to -control from severe 'refractory' asthma
American Thoracic Society /European Thoracic Society (ERS) task force -2013 guidelines	Categorising of severe asthma includes first confirming a diagnosis of asthma and secondly, treatment of co-morbid disease	Severe asthma is defined as asthma which requires treatment with high dose inhaled corticosteroids (ICS) doses in adults and children plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy.

1.3 IMPACT OF ADHERENCE TO INHALED MAINTENANCE THERAPY IN ASTHMA AND CLINICAL OUTCOMES

To achieve asthma treatment goals which include good asthma control, minimisation of risk of exacerbations, airflow limitation and side effects, adherence to ICS/LABA therapy is essential (34). Patients may continue to experience asthma symptoms and frequent exacerbations while on optimum ICS treatment because of on-going exposure to environmental triggers, co-morbidities or poor adherence and poor inhaler technique (35, 36).

Optimal adherence has been previously defined described using pill count, as the number of pills absent in a given time period divided by the number of pills prescribed by the physician in that same time period. A patient is deemed adherent if this percentage is greater than 80% (37). Studies have shown that a significant proportion of patients with severe asthma who are prescribed high doses of ICS are not adherent to their treatment. In a case series 50% of patients prescribed oral steroids were found to be non-adherent when assessed by plasma prednisone and cortisol concentrations (38). Furthermore, studies in adults and children in the USA and the UK have shown that the overall adherence to ICS was approximately 50% (39). Adherence rates to asthma medication have been shown to be variable across age groups, with rates of 49–71% observed in children and adolescents using objective measures of adherence (40). The methods used to assess adherence in these studies included, electronic monitoring (41), dose counting (42, 43), review of prescription refills and pharmacy refill data (44). Adherence rates in adult asthma patients have been shown to vary from 40% to 78% (45).

The relationship between poor inhaler adherence and asthma control has been well described. For example, in an observational study conducted by Ismalia et al. (46) performed on 19,126 Canadian asthmatic patients adherent to fluticasone propionate/salmeterol had lower asthma exacerbation rates (0.19 versus 0.23, $p<0.001$) while non-adherent patients had a 24% increased risk of having an asthma exacerbation (46). Both compliance {described as the medication possession ratio (MPR)}, and persistence to fluticasone propionate/salmeterol were assessed in this study. Compliance was calculated as the percentage of days covered by the

medication during the follow up period and patients were deemed compliant if the MPR was ≥ 80% and non-compliant if the MPR was <80%. Persistence was defined as having continuously renewed the fluticasone propionate/salmeterol prescription without a gap of more than 30 days. The patients who were adherent to salmeterol/fluticasone had lower rates of oral corticosteroid use, emergency room visits, general practitioner visits and hospitalisations (46). Hence, poor/sub-optimal adherence is associated with poor asthma control and increased risk of asthma exacerbations.

Non-adherence to inhaled medication, including inappropriate inhaler use, is associated with higher morbidity and mortality; frequent exacerbations; increased hospitalisation; and emergency department visits (47, 48). Health care costs per patient with severe asthma have been estimated to be higher than for those with type 2 diabetes, stroke, or chronic obstructive pulmonary disease (COPD) (49).

Furthermore, O'Neill et al. (49) has shown that adherence to ICS had a significant negative correlation with the number of emergency department visits, the number of fills of oral steroids and the total days' supply of oral steroid (49). Thus, poor adherence to ICS is associated with uncontrolled asthma, frequent exacerbations and subsequent frequent health care use.

Addressing non-adherence is effective if interventions to improve adherence are tailored to improve inhaler technique, promote regular use of the inhaled medication as well as addressing the cause of poor adherence. Despite the correct inhaler technique, patients may continue to have persistent symptoms and frequent exacerbations because of significant barriers that prevent them from taking their prescribed treatment. Some of these barriers include: lack of understanding of the disease; the perception that medicine is unnecessary; medication and health care costs; and the potential medication side-effects (49). Patients who experience side-effects are less likely to continue taking their asthma

medication. Higher doses of ICS may be associated with adverse events in some patients. Poor inhaler technique will lead to local side effects such as oral candidiasis and dysphonia (50). Patients may be concerned about systemic side-effects such as: skin thinning and easy bruising; an increased risk of osteoporosis, cataracts (51); and adrenal suppression which has been associated with high doses (≥1000 µg daily) of ICS (52-54). Therefore, assessment of ICS side-effects is crucial in achieving asthma control.

The COM-B, comprehension, opportunity, motivation and behaviour framework is one well-described method of understanding the causes of poor adherence. Therefore, assessment of patients presenting with severe asthma should include identifying and addressing the cause of non-adherence to inhaled maintenance medication.

1.4 ASSESSMENT OF POOR ADHERENCE IN ASTHMA IDENTIFICATION OF POOR INHALER ADHERENCE AND INHALER TECHNIQUE IN ASTHMA

Identifying non-adherence in clinical practice can be challenging because barriers to asthma treatment adherence vary from patient to patient and can be due to multiple factors such as patients' perceptions of benefits compared with adverse effects, patients' cultural beliefs and priorities, medication dosing and costs, an inadequacy of patient-physician communication and socio-economic factors (55).

1.4.1 Assessment of inhaler technique

The inhaler devices that are in current use are either pressurised metered dose inhalers (pMDI) or the dry powder inhalers (DPI). Despite the small aerosol particle size (0.5–10µm) of the pMDI (Figure 1-1) inhalers, approximately 40 to 45% of the inhaled dose fails to reach the airways even if the inhaler technique is flawless (56). This means that 40% of the inhaler is deposited in the oropharynx. Slow inhalation has been shown to reduce oropharyngeal accumulation of the drug (57), while deep breathing enables deposition in the peripheral airways (58, 59). Instructions to take the medication are as follows: patients should exhale fully, then inhale deeply for 5 to 10 seconds, activating the inhaler just after the onset of inspiration, and hold

breath for 6 to 10 seconds after inhalation (56), (Table 1-2). Failure to complete steps 4 to 8 leads to critical errors that affect aerosol delivery into the lungs. These critical errors include breathing in too quickly, stopping inhalation immediately after activation, activating the inhaler more than once in one inhalation, poor breath hold and poor coordination between activation and inhalation. Therefore, it is essential for the patient to slowly inhale the drug to decrease deposition of the aerosol in the oral cavity and larynx to allow drug deposition in the lower airways (60).

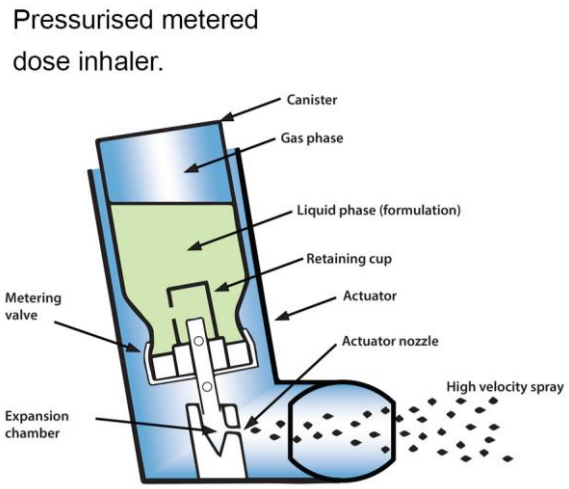


Figure 1-1 The Pressurised Metered Dose Inhaler

A schematic of a pressurised metered dose inhaler (pMDI), taken from the Global Asthma Report *2014*

Table 1-2 Pressurised Metered Dose Inhaler

The table shows the recommended steps for using a pMDI device.

Instructions on how to use Pressurised Metered Dose Inhaler	
1	Remove the cap from the inhaler mouthpiece
2	Hold the inhaler upright
3	Exhale fully away from the mouthpiece
4	Place the mouthpiece between your lips (keep tongue down and out)
5	Start to inhale slowly and deeply
6	Actuate the inhaler right after inhalation starts
7	Continue to breath in till your lungs are full
8	Remove the inhaler from your mouth and hold your breath for 10 seconds
9	Exhale

The DPIs are breath-activated and an example is a Diskus device which contains multiple doses in a foil strip (Figure 1-2). Inhaler technique is assessed by ensuring the patients follows the steps recommended to take the inhaler (Table 1-3) which include opening the mouthpiece, priming the inhaler, exhaling away from the mouthpiece, putting the mouthpiece in between the lips, inhaling forcefully and rapidly, and holding the breath for 10 seconds to ensure adequate aerosol deposition. Critical errors include failure to prime the drug, exhaling into the device, low inspiratory flow (61). Humidity may cause de-aggregation of the dry powder mix and hence reduced drug deposition (62). Given the different inhaler devices it is crucial to provide education on inhaler technique and on-going assessment and correction of inhaler technique is required to ensure patients are receiving adequate therapy.

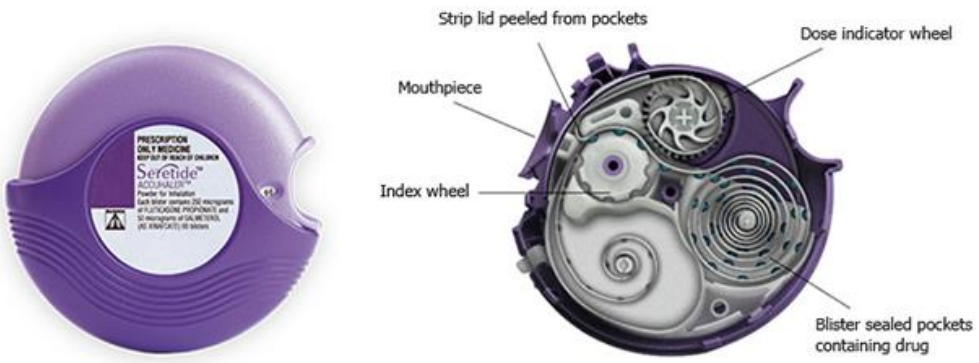


Figure 1-2 The Dry Powder Inhaler

The figure shows a diagram of the Diskus Seretide Dry Powder Inhaler (DPI). Image retrieved from https://www.seretide.co.nz/copd/accuhaler.html

Table 1-3 Dry Powder Inhaler

The table shows the recommended steps for taking a DPI device.

Instructions on how to use Dry powder inhaler	
1	Expose the Mouthpiece
2	Hold the inhaler in recommended position for specific inhaler device
3	Prime the inhaler
4	Exhale fully away from the mouthpiece
5	Place the mouthpiece between your lips (keep tongue down and out)
6	Inhale Rapidly and forcefully
7	Continue to breath in until your lungs are full
8	Remove the inhaler from your mouth and hold your breath for 10 seconds
9	Exhale
10	Cover the Mouthpiece

1.4.2 Methods of assessing inhaler adherence in asthma

There are different tools that are used to assess inhaler adherence. These include self-report tools such as electronic or paper diaries and surveys. The disadvantage of self-report is that it is dependent on a patient being able to recall taking an inhaler and can also be biased by misinformation given by the patient to please a healthcare provider (63-65). These methods are also limited by their reliability with little published data on same (66). Inhaler dose counting is another method of assessing inhaler adherence. However, inhaler dose counting does not provide information when the drug was taken and is affected by dosing dumping, refill of prescription data and pharmacy dispensing data. Pharmacy dispensing data has the advantage of giving a rough estimate of the persistence of medication use; conversely, prescription dispensing data does not provide information on how and when the individual has used their medication.

Another technique that can be used to assess adherence in asthma population is Fractional Exhaled Nitric Oxide (FeNO) suppression. Nitric oxide (NO) in the human airways is formed from l-arginine and oxygen catalysed by the nitric oxide synthases (NOS) (67). Type II NOS, which is localised to the airway, alveolar epithelium, and alveolar macrophages is inhibited by glucocorticoids (68). Higher levels of FeNO have been detected in patients with asthma (69) and, decreased FeNO levels have been detected during an exacerbation when patient is on glucocorticoid therapy (70). Therefore, FeNO can be used in clinical practice as a surrogate marker for T helper cell type 2 (Th-2) or eosinophilic airway inflammation (71, 72). FeNO levels >50 has been shown to indicate eosinophilic inflammation and the likelihood of good response to corticosteroids while levels <25 indicate non-eosinophilic inflammation and the possibility of poor response to corticosteroids (72). FeNO monitoring can be used to identify ICS therapy non-adherence (73). In a study published by McNicholl (73), patients with a high FeNO level were followed for five consecutive days receiving directly observed inhaled steroid therapy. Patients who were deemed non-adherent, based on previous pharmacy refill records, had a significantly higher reduction in their FeNO level than those who were adherent,

suggesting that FeNO may be used to differentiate patients who have uncontrolled severe 'refractory' asthma and those have uncontrolled asthma but are not adherent (73). Hence, FeNO monitoring helps identify patients with eosinophilic inflammation, patients who are likely to be steroid resistant and patients with suboptimal adherence.

Advances in methods of assessing adherence have led to development of electronic monitors. These devices such as the doser (74), records the number of inhaler actuations without recording the time of use. Some of these devices include the SmartTrack, SmartMist,MDILog (75, 76), Smartinhaler Tracker (77)and Propeller device(78). Sensors record the date and time of each inhaler actuation and have the advantage of in-built missed doses reminders based on the patient's treatment. The data can be uploaded remotely to a webserver (79). Julius et al. tested the accuracy of the Doser, MDILog and the SmartMist in recording actuations. All devices had high levels of accuracy, however the SmartMist was 100% accurate (76). The Doser and MDILog occasionally recorded additional actuations. Chan et al. (80) reviewed the currently available electronic inhaler monitors for inhalers(81). The accuracy of some of these devices, when compared to written diaries, is between 90% and 100%, with (76) failure rates ranging from 0% to 21%. The advantage of these monitors is that the data collected can be used to identify poor adherence. However, the electronic monitors come at a high price and their cost-effectiveness and their relationship with clinical outcomes in different patient population has not yet been studied (81).

The INhaler Compliance Assessment (INCA) device (Figure 1-3) has been developed for the Diskus inhaler by the INCA RCSI and Trinity College research team. Unlike the previous electronic monitors which only identify when an inhaler has been use, this technology has the advantage of establishing both when and how well an individual has used their inhaler. Thus, both the habit of use and inhaler technique are assessed and therefore can be addressed. Analysis of the audio recording yields information on whether the inhaler was opened, if the inhaler was primed and if

there was an inhalation. The device also allows identification of the peak inspiratory flow (PIFR) during inhalation, as well as pre-identified inhaler errors such as exhalation after drug priming, or multiple actuations or multiple inhalations. The INCA device has been used in two randomised controlled trials (82, 83) in primary and secondary care to promote adherence. In these studies, both the cost effectiveness of the INCA adherence education intervention as well as the use of the INCA device data to guide clinicians in decision making regarding either escalating or stepping-down therapy has not been investigated. Therefore, there was a need to conduct a study to investigate the cost effectiveness of the INCA device and to investigate whether prior known adherence from the INCA device can be used to guide clinical decision in optimising asthma therapy.

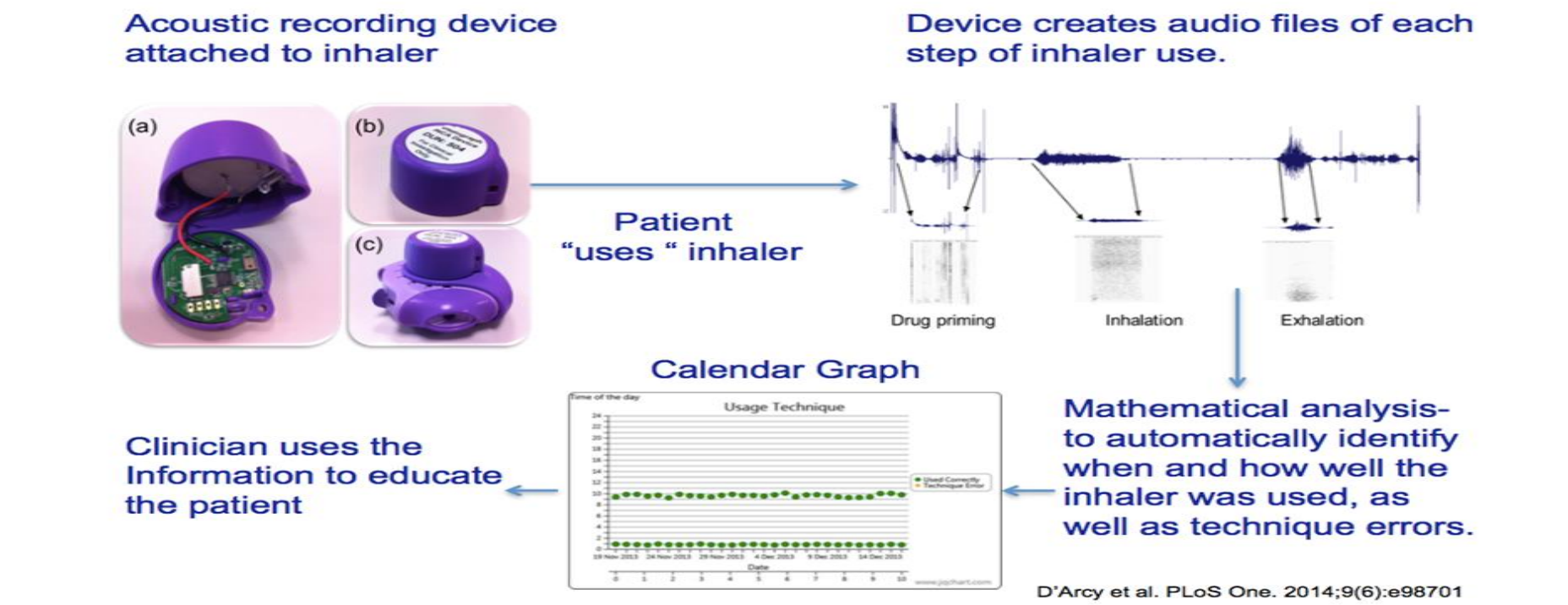


Figure 1-3 The Inhaler Compliance Assessment (INCA) device.

Figure 1-3 illustrates the INCA system, which is an audio recording device, fitted to a Diskus inhaler. The device consists of a small battery-powered microphone, solid-state memory storage and a microprocessor. Opening the inhaler initiates an electronic acoustic recording of the audio associated with an inhalation and exhalation during the use of an inhaler, and the audio recording ends when the inhaler is closed. The audio files are time-stamped and

stored on a memory platform until the device is uploaded to a computer. Analysis of this information provides objective information on both when and how well the individual used the inhaler.

Once non-adherence is identified, clinicians must provide adherence interventions to address non-adherence. The underlying causes of non-adherence must be considered to address non-adherence efficiently. Different underlying mechanisms of non-adherence have been described. The 2003 World Health Organization adherence report concluded that there are four mechanisms of non-adherence. These include: erratic non-adherence, which is defined as forgetting to take the inhaler; intelligent non-adherence which is a conscious decision not to take medication due to side-effects or disbelief that drugs are efficient, and unwitting non-adherence (lack of knowledge about the disease and the need for taking medication) (84). The different mechanisms highlight the significance of identifying the underlying cause of non-adherence in conjunction with using objective methods of assessing adherence to provide adherence interventions that are tailored to the specific needs and beliefs of each patient.

1.5 AIRWAY INFLAMMATION IN ASTHMA AND BIOLOGIC THERAPY

The most common underlying inflammation in asthma is Th2 type 2 inflammation. This was first described in a murine model by identification of an adaptive immune response which is characterised by the release of a distinct set of interleukins (IL), including IL-4, IL-5, IL-9, and IL-13, from Th2-type cluster of differentiation 4 ($CD4^+$) cells, which mediate the pathogenesis of allergic asthma (85, 86). Following exposure to an allergen, thymic stromal lymphopoietin (TSLP), an IL-7–like cytokine is produced by airway epithelial cells, fibroblasts, and mast cells. This results in activation and maturation of antigen-presenting dendritic cells in response to TSLP. Mature dendritic cells stimulate the differentiation of naïve $CD4^+$ T cells into Th2 cells. This leads to a production of cytokines, such as IL-4, IL-5, IL-9, IL-13, as well as tumour necrosis factor (TNF). Th2 cytokines mediate airway eosinophil and mast-cell recruitment, B-cell IgE isotype class switching, and mucus secretion (

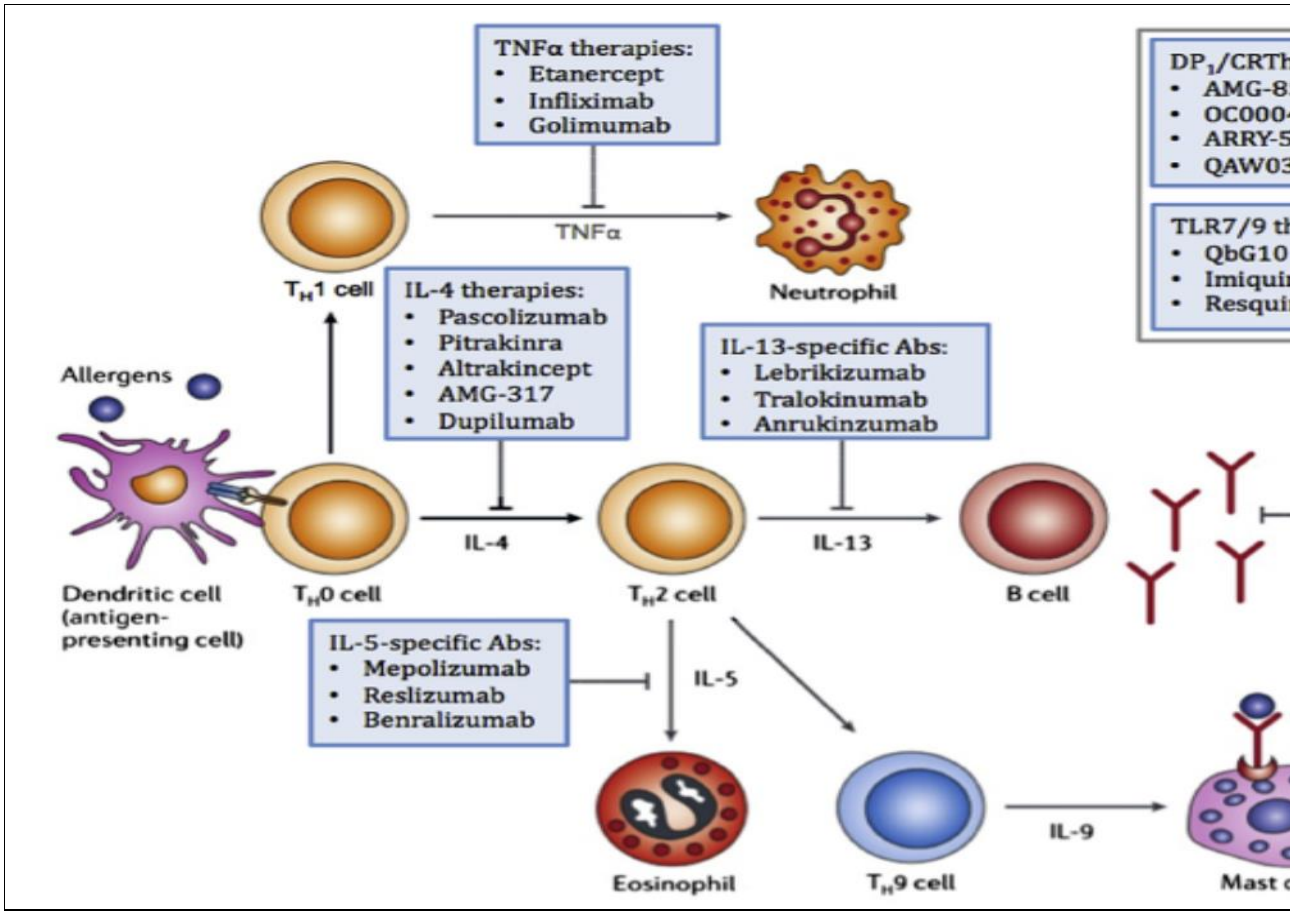


Figure 1-4). Epithelial cells also secrete alarmins such as IL-33, which induces the differentiation of both innate lymphoid class 2 (ILC2) cells. These cells release IL-5 and lead to an alternative recruitment of eosinophils that does not involve the typical allergic inflammation pathway.

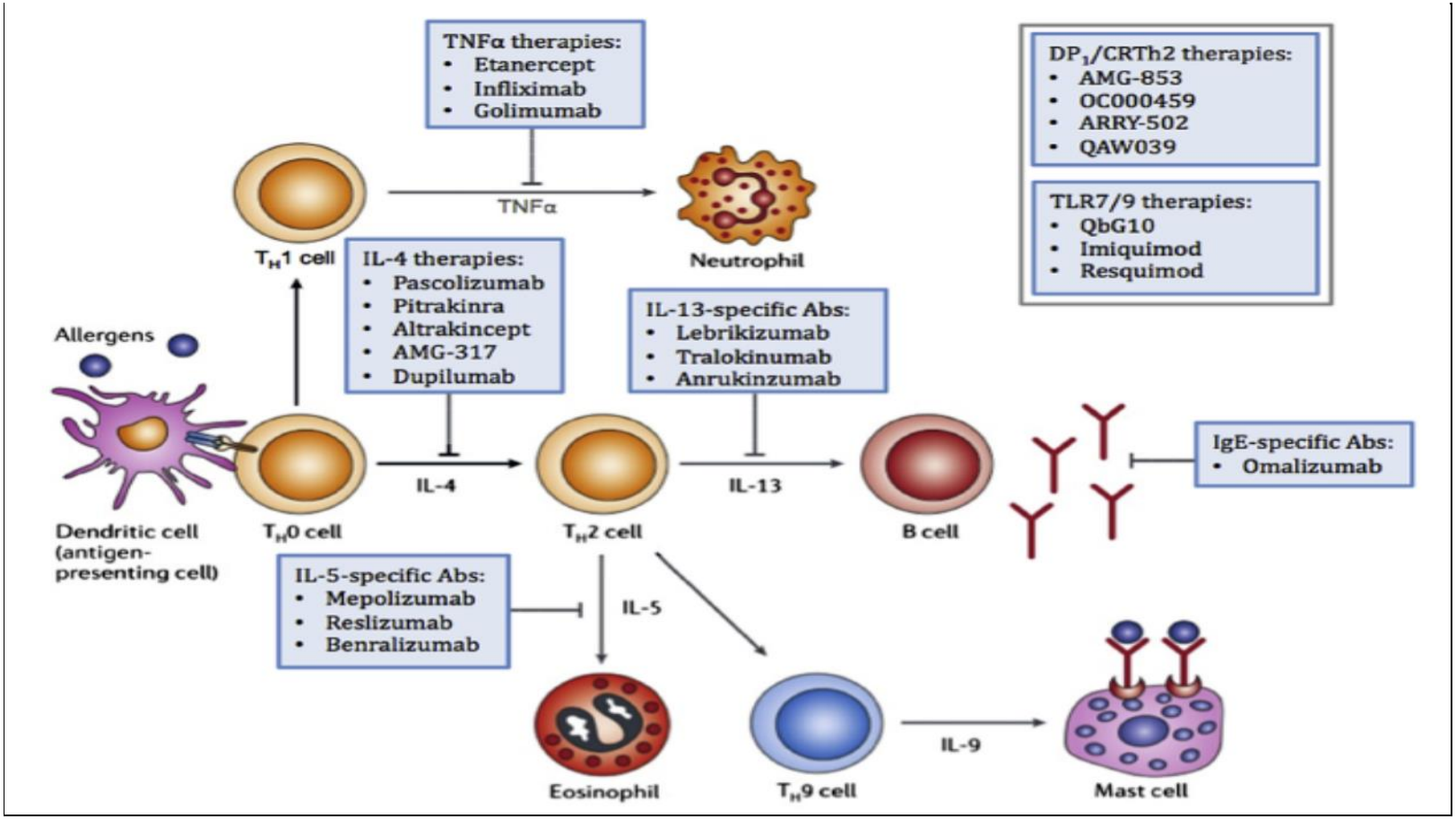


Figure 1-4 Pathophysiology of type 2 inflammation in asthma (87)

The figure above illustrates the pathophysiology of type 2 inflammation in the human airway, highlighting type 2 cytokine and IgE pathways. including the available biologic agents targeting IgE, IL-, IL-13, IL-4 receptor a and TSLP.

APC, Antigen-presenting cell; ILC2, type 2 innate lymphoid cell; iNOS, inducible nitric oxide synthase.

There have been advances in developing biologic therapy targeting Th2 cytokines. The first of such targeted therapy is humanised monoclonal antibodies against IgE, which has been thoroughly investigated and numerous studies have shown significant reductions of oral steroids, improvement in the asthma-related quality of life, and increase in lung function (88-90). Mepolizumab, a humanised monoclonal antibody against IL-5 selectively inhibits eosinophilic inflammation (91-93) and has been shown to reduce exacerbations and the need for treatment with systemic glucocorticoid in patients with eosinophilia (94-96) as well as improving asthma control (95, 97). Reslizumab, a humanised anti-IL-5 monoclonal antibody that binds circulating IL-5 preventing the binding of IL-5 to its receptor (98) improves lung function (FEV1) and asthma control (ACQ-7 scores) in patients with eosinophils ≥400 cells/mL (99, 100). Dupilumab, a human anti-interleukin four receptor α monoclonal antibody that blocks both IL-4 and IL-13 signalling, has been shown to be successful in reducing exacerbations as well as improving lung function and asthma control (101, 102). Surrogate markers that drive type 2- inflammation have been used to guide biologic therapy; for example, eosinophil levels for targeted anti-IL5 therapy, IgE for omalizumab and in periostin-high patients' lebrikizumab was efficacious in reducing the rate of asthma exacerbations and improving lung function compared with periostin-low patients (103). In a study by Castro et al. (102) patients with a higher baseline FeNO showed a greater response to Dupilumab and, therefore, had lower exacerbation rates and had improved FEV1 (102). A 'Type2-Low asthma' or non-eosinophilic asthma, characterised by minimal response to steroid therapy has been identified (104-107). New therapeutic approaches that target Type 2 low asthma are being investigated. For example, Sch 527123, a CXCR 1/2 receptor antagonist was found to improve airway inflammation in animal models (108, 109) and CH527123, a selective CXCR2 receptor antagonist, has been to proven to reduce neutrophils in asthma patients with neutrophilia (110). Recognition of a Type 2 low or high component of airway inflammation in severe asthma allows targeted biologic therapy.

1.6 DISCUSSION

In this chapter, I have indicated that a systematic evaluation of patients with severe asthma is required to identify the reasons for poor asthma control. A thorough clinical history which includes the age of onset of asthma, aggravation of asthma such as Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and environmental triggers must be reviewed. Concurrent asthma co-morbid diseases such as atopic dermatitis, food allergy, allergic rhinitis, chronic rhinosinusitis, gastroesophageal reflux disease and asthma medication history should be assessed and treated. Asthma diagnosis should be confirmed using additional diagnostic tests such as pre- and post-bronchodilator spirometry, bronchial provocation tests if warranted. Further tests including skin allergy tests or blood test panel for specific IgE to common airborne allergens, sputum eosinophilia, and FeNO provide additional information on the asthma phenotype and may predict response to biologic therapy. Potential non-adherence should be assessed and addressed and if patients have persistent poor asthma control despite adequate adherence then advancing therapy to further therapy such as an immune modulating therapy such as a “biological treatment” will be appropriate.

1.7 AIMS AND INTENTIONS FOR THE THESIS

This thesis aims to determine the importance of assessing inhaler adherence in patients with uncontrolled severe asthma as an aid to clinical decision-making. I have discussed the relationship between non-adherence and clinical outcomes as well as the significance of identifying asthma inflammatory biology in patients with ‘refractory’ asthma. In the next chapter, I will assess how adherence to maintenance therapy is conducted in clinical trials. To understand the impact of inhaler adherence on the clinical outcomes in patients with severe asthma the following intentions were set:

1. To review how inhaler adherence is assessed in clinical trials of "add-on” treatment interventions conducted in patients with severe asthma (Chapter 2). From this, I can identify whether adherence was assessed and patients

with ‘refractory’ asthma were identified and recruited to into the clinical trials.

2. To evaluate the effect an education programme targeting inhaler adherence (both the habit of use of inhaler and inhaler technique) has on the persistence of good inhaler adherence in a cohort of severe asthma patients (Chapter 3). I also evaluate the use of the INCA device adherence data and Th2-biomarkers to guide clinicians in optimising asthma treatment.

1.8 CONCLUSION

A systematic evaluation of patients with severe asthma is required to identify reasons for persisting symptoms and frequent exacerbations. Adjusting pharmacological and non-pharmacological treatment in a continuous cycle that involves assessment, treatment and review of response is the mainstay of control based asthma management (4). Treating modifiable risk factors, assessment of adherence, in addition to reviewing and correcting inhaler technique errors is paramount in the management of patients with severe asthma. Assessing treatment response, aiming to decrease or escalate therapy as well as addressing patients concerns and medication adverse effects is vital to maintaining optimal compliance with maintenance therapy. Disease phenotype may significantly affect the choice of diagnostic tests and long-term prognosis, and, most importantly, predict responsiveness to specific pharmacotherapies.

I have discussed the relationship between non-adherence and clinical outcomes as well as the significance of identifying asthma inflammatory biology in patients with ‘refractory’ asthma. In the next chapter, I will assess how adherence to maintenance therapy is conducted in clinical trials.

Chapter 2. Systematic Review

SYSTEMATIC REVIEW OF INHALED CORTICOSTEROID AND LONG ACTING BETA-ADRENOCEPTOR AGONIST THERAPY ADHERENCE REPORTING AND MONITORING IN CLINICAL TRIALS OF SEVERE ADULT ASTHMA DRUG TREATMENTS

2.1 INTRODUCTION TO THE CHAPTER

A combination therapy of inhaled corticosteroids and long-acting beta-agonist (ICS/LABA) is recommended therapy for patients with severe asthma (111). Approximately 10% of asthma patients remain 'difficult to control' despite this therapy (2). Assessing adherence can be challenging in clinical practice and in clinical trials because barriers to asthma treatment adherence vary from patient to patient and can be due to mutliple factors such as patients' perceptions of benefits compared with adverse effects, patients' cultural beliefs and priorities, medication dosing and costs, inadequacy of patient-physician communication and socio-economic factors (112-114). Identifying non-adherence in patients with severe asthma who remain 'difficult to control' is essential, given current available expensive biological therapies but it also helps to define mechanisms and phenotypes of 'refractory' asthma (55).

2.2 BACKGROUND

In patients with asthma, Steps 3 and 4 of the GINA management guidelines (Appendix 11) includes treatment with ICS with the addition of LABA as maintenance therapy (low dose ICS in Step 3 and medium to high dose ICS in Step 4). Addition of an inhaled LABA to treatment with an ICS alone has been proven to reduce the risk of exacerbations and improve lung function (115, 116). Patients with persistent symptoms or exacerbations while on Step 4 therapy despite good adherence are considered to have 'refractory' asthma and should be considered for Step 5 treatment. There are many options for Step 5 treatment: these include a monoclonal anti-IgE antibody therapy; a monoclonal anti-IL5 therapy; the surgical intervention bronchial thermoplasty; or additional medications such as tiotropium or low dose oral corticosteroids (≤7.5 mg/day prednisone equivalent) (117). Which one of these therapies is chosen to be used requires deep biological assessment and specialist input due to the potential cost and complexity of these therapies.

In Chapter 1, I described the importance of adherence and inhaler technique in the management of patients with severe asthma. I explained how uncontrolled asthma

which can be due to poor adherence to therapy leads to increase patient morbidity and drives asthma costs, directly through wasted medication as well as indirectly through costs associated with extra care from inadequately controlled symptoms. I also indicated that by adhering to established asthma management guidelines that asthma costs might be reduced by addressing adherence to therapy as well as ensuring that treatment escalation with biologic treatment is appropriately prescribed for patients with 'refractory' asthma. I also described the methods of assessing adherence both in clinical practice as well as in clinical trials. What this means in practice is that clinicians caring for severe asthma patients assume that their patient's prior adherence to ICS/LABA therapy was optimal and hence inappropriately escalate treatment with the available expensive biologic therapies.

There are several design issues in the trials of 'add-on therapy' for patients with (add on therapy including biologic therapy such as anti-IgE therapy anti-IL5 and anti-IL13 therapy; anti-tumor necrosis factor therapy; and bronchial thermoplasty) severe asthma, in relation to monitoring of adherence to maintenance ICS therapy (118). Firstly, there is a potential for a "placebo response" in some of the endpoints used in these trials. Placebo response is an essential but little understood tendency for subjective signs and symptoms to respond to an apparent therapy that has no pharmacological activity (119). While there is no literature on the placebo response in trials of 'add-on therapy' for patients with severe asthma, it is recognised to be a feature of subjective measures such as quality of life scores among patients with asthma (120). As this is assumed to occur systematically, randomisation mitigates this response as does the use of objective measures, such as spirometry and health care use. A period of run-in is often included in the study protocol, although this may be too short to ensure that the lag between treatment adherence and outcomes such as exacerbations or symptom control becomes apparent. It should be noted that it is difficult to make the diagnosis of exacerbation across healthcare systems.

Another issue in the design of these studies is that there is a potential for the Hawthorne effect, which during clinical trial patients may become more adherent to their therapy (121). Given how vital adherence to treatment is, there is a potential that some participants invited to participate in a clinical trial of a new agent for asthma may not have been adherent to their usual medications. If adherence to currently prescribed medications is not measured before recruitment, it is possible that patients may be uncontrolled purely due to poor adherence. Hence, they may not be suitable for the trial as they have "'difficult to control'" rather than 'refractory' asthma. Despite randomisation mitigating the effects of the Hawthorne effect, a small amount of variance that is introduced by the Hawthorne effect exist and may contribute to wider standard deviations in the study outcomes with subsequent insignificant study results.

An additional problem of clinical trials of add-on therapy is that, during a clinical trial, if adherence to the already prescribed GINA Step 3/4 therapy (low dose to medium dose ICS and LABA) is not assessed at baseline and not monitored throughout the study, the outcomes of the study might be difficult to interpret accurately. An assumption that adherence is optimal (≥80%) is made if adherence is not assessed at baseline. However, this may not be the case. Using the INCA device, an objective method of assessing adherence, Sulaiman et al. (82) has shown baseline mean adherence rate of 65±28. This means that participants with poor adherence will be enrolled into the study of add-on therapy if adherence is not assessed. Consequently, the study may be underpowered to detect the true treatment effect size because of the inclusion of ''difficult to control' patients" or very large, expensive studies will need to be performed (122). Furthermore, during the study, participants may also become less adherent to their previously prescribed ICS therapy; this may be important as add-on therapy studies have involved molecules that target the same molecular pathways as ICS, potentially meaning that there may be differential rates of poor adherence between active and control groups. Importantly, the true efficacy of an investigational agent may be affected because, among people with lower adherence rates, the variance and,

hence, standard deviation of clinical endpoints will be higher which leads to larger sample sizes needed for recruitment. Therefore, adherence to currently prescribed therapy in asthma 'add-on therapy' studies needs to be assessed and monitored both at baseline and throughout the study to accurately interpret outcomes in clinical trials.

In this chapter, I describe a systematic review, which assesses how adherence to maintenance inhaled asthma therapy was evaluated in clinical trials of add-on drug treatments conducted in patients with severe adult asthma. I also performed a modelling experiment to assess the effect of assessing adherence to ICS/LABA on study end-point measures were it to have been that only adherent patients had been enrolled in the published studies.

2.3 OBJECTIVES

The aim of this systematic review was to review all available, published randomised controlled clinical trials (RCTs) conducted in patients with severe asthma to assess how adherence to ICS/LABA therapy was reported. I was particularly interested in identifying whether adherence to ICS/LABA therapy was conducted as part of the screening or the run-in period and assess whether monitoring of this therapy was performed during the study. Also, I evaluated the outcome changes in the placebo-treated groups to identify the effect of the placebo effect. To assess the effect of adherence on clinical outcomes, I modelled the impact of varying levels of adherence at different phases of the study to calculate new standard deviations adjusted for adherence assessment.

2.4 HYPOTHESIS:

We hypothesised that prior and current adherence to combination therapy of ICS and LABA is under-assessed and poorly reported in clinical trials that assess the effect of "add-on" drug treatment for patients with severe uncontrolled GINA stage

3/4 asthma. Furthermore, studies in which adherence were assessed during the run-in phase of the study and throughout the study would be adequately powered to achieve real changes in outcomes in favour of the active treatment.

2.5 PRIMARY OUTCOME

The primary outcome was the description of how adherence to currently prescribed ICS/LABA was assessed and monitored throughout the study (i.e., from the run-in phase until the end of the study).

2.6 SECONDARY OUTCOMES

The secondary outcomes were:

1. A comparison of the effect of the active intervention on clinical outcomes of studies in which objective measures of adherence were used and studies where either subjective methods were used, or adherence was not monitored. This was conducted by performing a between group (active add-on treatment group and placebo add-on) mean change from baseline for the outcomes, forced expiratory volume in one second (FEV1), peak expiratory flow (PEF), asthma control questionnaire (ACQ) and asthma quality of life (AQLQ).
2. Assessment of the difference of changes in the clinical outcomes in the placebo groups in the studies included in the review. A comparison of the mean pre-bronchodilator FEV1, PEF, ACQ, and AQLQ in the control (placebo) group, at baseline and the end of the study was conducted across all the clinical trials to identify the placebo effect.
3. A model of the effect of optimal adherence to salmeterol/fluticasone propionate therapy during the run-in period, and during the study was constructed and applied to the studies reported in the systematic review. A model of the Hawthorne effect was illustrated to describe the variance introduced by the Hawthorne effect.

2.7 ANALYSIS

Descriptive statistics were used for reporting the primary outcome (assessment and reporting of adherence to ICS/LABA therapy). A random effect meta-analysis comparing the mean change from baseline for the outcomes: FEV1, PEF, ACQ, AQLQ, between the placebo and intervention groups was conducted across all the studies that assessed adherence to ICS/LABA therapy. Analyses were conducted using Review Manager 5.3 software (123). Pooled estimates with 95% confidence intervals (CIs) of the evaluated outcome measures were calculated and reported. The I^2 statistic was examined to describe the proportion of the variability in the results of studies included in the meta-analysis. The I^2 statistic describes the percentage of total variation across studies that are due to heterogeneity rather than chance (124). The I^2 statistic ranges between 0 and 100% and values of ≥75% are considered of high heterogeneity. A comparison of the mean ACQ, AQLQ, pre-bronchodilator FEV1 and PEF in the control (placebo) group, at baseline and the end of the study, was also conducted using random effects meta-analysis.

2.8 METHODS

The protocol for the systematic review has been published in Prospero. (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015029611). The methodology for this systematic review was conducted using the Cochrane Handbook for Systematic Reviews of Interventions (125).

2.8.1 Criteria for considering studies for this review

2.8.1.1 *Types of studies*

Parallel and cross-over randomised controlled trials (RCTs) full-text publications that were written in the English language were included in this review. Studies that were not eligible for inclusion were review articles, unpublished studies, case reports, audits, guidelines, editorials, conference abstracts, letters and comments and studies where only the abstracts were available.

2.8.1.2 *Types of participants*

Adolescents aged ≥12years of age or adult patients with severe asthma who were prescribed either ICS or a combination of ICS and LABA as maintenance therapy were included. Various definitions of severe asthma were accepted if they were based on clinical diagnosis plus confirmed objective criteria consistent with established guidelines.

2.8.1.3 *Types of interventions*

Studies were included if they assessed any drug intervention as add-on therapy to any dose of ICS and LABA combination therapy or medium or high dose ICS therapy without LABA therapy, consistent with GINA therapy step 3 or 4.

2.8.2 Search methods for identification of studies

2.8.2.1 *Electronic searches*

Two independent authors identified studies from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science and PsycINFO. Details of the specific search strategies for the relevant databases are shown in Appendix 1. Databases were searched for records published in the English language from 1st January 1995 until 30th November 2015.The search was conducted from the 25th November 2015 until 25th January 2016. A second search was conducted on the 21st June 2017 to include articles published between 1st December 2015 and 30th June 2017.

2.8.2.2 *Searching other resources*

Two independent authors extensively hand-checked the reference lists of all retrieved primary studies and review articles to supplement the list of the selected studies.

2.8.3 Selection of studies

Two independent authors searched the databases for the potential trials and duplicates records were removed. A dedicated online systematic review software programme (www.covidence.org) was used to extract some of the data (screening of articles and assessing the risk of bias). Two review authors independently screened titles and abstracts for the inclusion of all potential trials. Full-text study publications were retrieved and screened by two independent authors. Studies for inclusion were identified and reasons for exclusion of ineligible trials were recorded. Disagreements were resolved by consensus and discussion with a third author. Trials with multiple reports were collated to ensure that each trial was the unit of interest in the review. The selection process was recorded by completing a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (126).

2.8.4 Data extraction and management

Two independent review authors extracted data. The initial plan was to use www.covidence.org to retrieve study characteristics and outcome data, but this was time-consuming, and hence Microsoft Excel was used to perform data extraction. Missing data were obtained by directly contacting the authors whenever possible or other registries if the trial was registered, i.e. www.clinicaltrials.gov.

2.8.5 Assessment of bias in the included studies

Two authors independently assessed the risk of bias for each trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (125) and we resolved disagreements by discussion. The risk of bias was assessed according to the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting and other bias, within each included trial.

2.8.6 Summary of findings table

A 'Summary of findings' table was created using pre-specified outcomes such as adherence measurement/method of assessing adherence used and reporting of ICS/LABA.

2.8.7 Estimating the effects of assessing adherence to ICS/LABA therapy on clinical outcomes

I derived a model of the potential effect of additional variance introduced by the absence of assessing adherence to ICS/LABA on the primary outcomes of studies included in the systematic review. To estimate the effects of variations in adherence to maintenance therapy on FEV1, first I had to estimate the mean change in FEV1 and standard deviation that would be achieved if adherence was assessed objectively.

The mean change in FEV1 was obtained from an RCT comparing salmeterol/fluticasone propionate and placebo (127). Shapiro et al. (127) reported a mean change in FEV1 at week 12 of 0.48 litres with a standard error of 0.05 giving a standard deviation of 0.45 litres (127). Shapiro et al. assessed adherence to salmeterol/fluticasone propionate using paper diary and dose counting to assess adherence during the screening phase and the 12 weeks duration of the study. Considering that the reported dose counts mean adherence rates of 91% to 95% across treatment groups, it is likely that adherence was sub-optimal, and so these results may be an under-estimate of the true effect of salmeterol/fluticasone propionate on FEV1. These adherence rates are consistent with the dose counts observed in Sulaiman's study (82). To estimate the 'true' mean change in FEV1, I assumed that the actual adherence rate will be similar to Sulaiman's (82); i.e. mean actual adherence rate of 65±28%; (' سي πϕ ,υ„ سي πϕ at baseline. Assuming a linear relationship between salmeterol/fluticasone propionate adherence rate and the mean change in FEV1, then the mean change in FEV1 is equal to the "true effect" multiplied by the salmeterol/fluticasone propionate adherence rate.

Therefore, the mean change in FEV1 adjusted for actual baseline adherence rate of 0.65 gives a 'true' mean change in FEV1 at week 12 of

Additionally, the subsequent corrected standard deviation is

$$= \{0.45^2 - (0.3^2 \times 0.74^2)\} \div \{0.3^2 + 0.65^2\} = 0.3$$

The estimated 'true' mean change in FEV1 adjusted for baseline adherence rate of 0.65±0.3 is estimated as 0.74±0.55 litres where = 0.74 and = 0.55. I used this estimate to model the effects of adherence variations on FEV1 adjusted for objectively measured adherence.

2.8.7.1 *Month-to-month variability in the absence of adherence monitoring throughout the trial*

I conducted a model of the variance introduced into study outcomes due to within-subjects' variations in month to month adherence to ICS/LABA. Sulaiman et al. (82) found that, while the mean change in adherence from month to month was negligible, there was a large standard deviation in this change, with a mean absolute change of more than 20% from month 1 to month 3. The actual adherence decreased by 0.8%± 31.3% from month 1 to month 3 in the control group. Assuming that the mean change is zero there is still a large variability that can affect the significance of the study results. Assuming a mean change in adherence of zero, the standard deviation of the within-subject month to month variation in adherence can be used to estimate the additional adherence introduced by the absence of assessing adherence throughout the study. Using , the estimated 'true' change in FEV1, = 0.74 and =

0.55 and the standard formula for the variance of a product the additional variance in outcomes attributable to adherence variations can be estimated. The estimated month to month variance introduced into FEV1 outcomes is

$$= 0.0832$$

This gives an additional variance of 0.083. When this variance is compared to study variances in the range 0.01 to 0.21, it constitutes a considerable extra source of variance which may greatly reduce study power if it is not accounted for during power calculations. To illustrate the potential impact of this additional variance component on study outcomes, we extracted reported variances (SD-squared) of all studies in the systematic review and obtained adjusted variance estimates by subtracting our estimate of the variance due to adherence changes. I then produced forest plots and conducted meta-analyses to compare the results with those using the uncorrected variance values.

2.8.7.2 *Regression to the mean*

Using the data from Sulaiman's study (82), the difference in adherence between month 3 (M3) and month 1 (M1) for the patients who achieved ≥80% adherence at baseline (59 of 170 patients) was calculated. On average, from M1 to M3 adherence decreased significantly (mean change -8.4± 21.17%) giving

Using the estimated 'true' mean change in FEV1 (0.74±0.55 litres where 0.74 and $\sigma = 0.55$) and the mean change adherence rate for the patients who achieved adherence rate of ≥80% the estimated additional variance introduced by assessing adherence only at baseline mean is calculated below:

The estimate of the variance introduced into the FEV1 outcome is

The additional variance in FEV1 due to the absence of monitoring adherence to ICS/LABA is 0.0402.

This additional variance was subtracted from the variance in each individual study to calculate the new standard deviations (example below).

Example: In the Bjermer study (128) the mean change in FEV1 from baseline in the Reslizumab group was (0.286±0.553). The estimate of the variance introduced into FEV1 outcome in the absence of adherence monitoring was 0.0402. The FEV1 variance is:

$\{(0.553)^2 - 0.0402\} = 0.265576$

And this gives a new standard deviation of 0.54 (square root of 0.265576).

2.9 RESULTS

2.9.1 Description of studies

2.9.1.1 *Results of the search*

8667 articles were retrieved by electronic search (Appendix 1) conducted in January 2016. An additional 19 articles were identified after conducting an electronic search on the 21st June 2017. The study flow is demonstrated in Figure 2-1. 4350 duplicate records were excluded, 4336 records were screened for eligibility of which 4007 were excluded and 329 full–texts articles were assessed for eligibility. Eighty-seven RCTs (89, 94-97, 99-101, 103, 129-203) were deemed eligible for inclusion, and 242 were excluded with reasons documented.

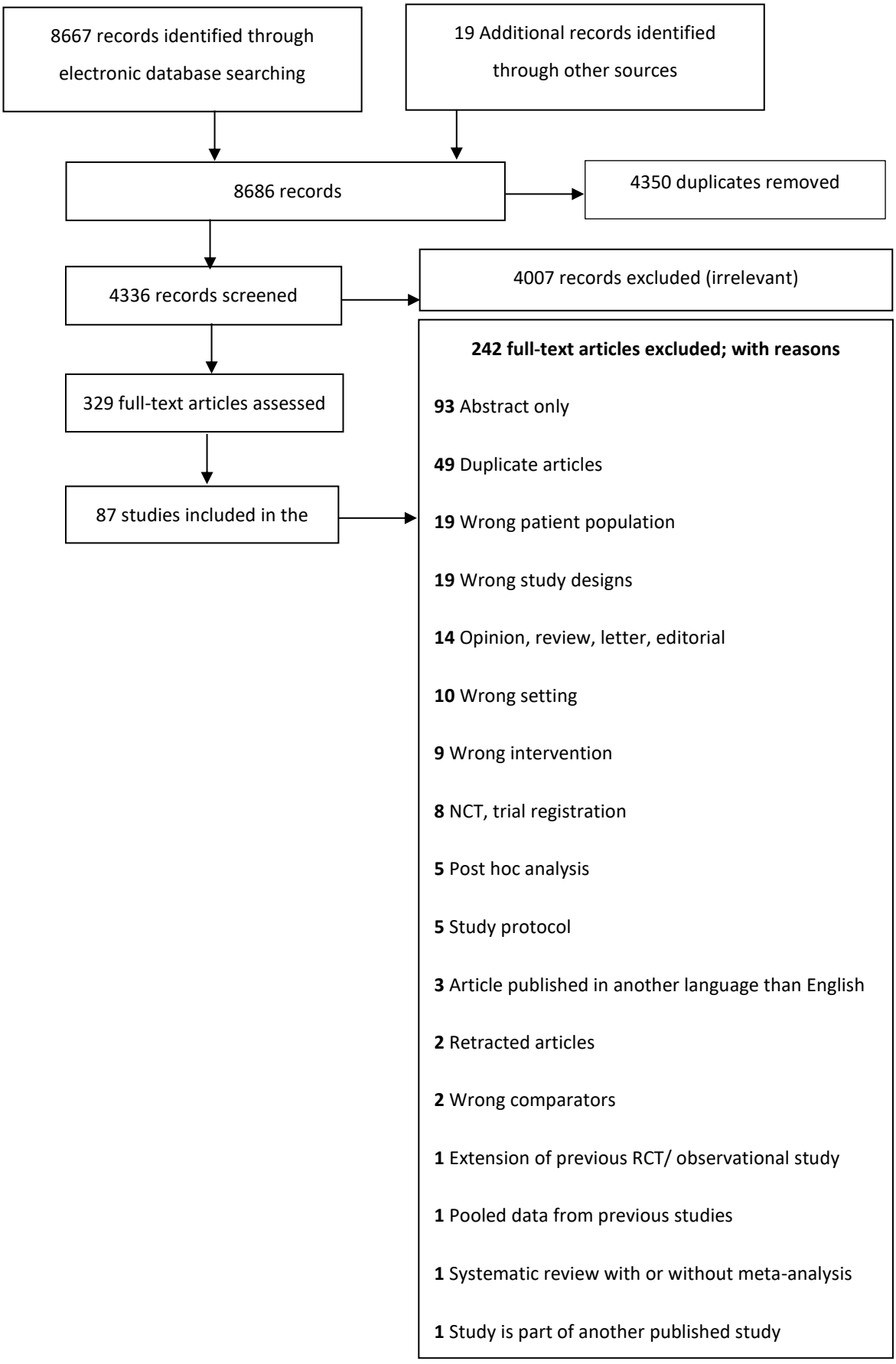


Figure 2-1 Flow diagram of the literature search

2.9.1.2 *Characteristics of included studies*

A detailed review of the design, duration, inclusion and exclusion criteria, as well as data collected for the 87 trials, is outlined in Appendix 2 and below.

2.9.1.3 *Study design*

All included trials were RCTs that compared any drug intervention to placebo, as an additional treatment to either medium dose ICS therapy or high dose ICS and LABA combination therapy. In most trials, (n=83) the study design was a parallel group, except for four in which the design was crossover design (132, 150, 164, 190). There was a wide range in the duration of the trials which lasted from 2 to 52 weeks, the mean length of the studies was 27 (16.1) weeks.

2.9.1.4 *Study Population*

Only trials involving adolescents aged ≥12 and adults were included. All the participants had a confirmed diagnosis of asthma (Appendix 2)**.** The severity of asthma varied among the trials and was based on established guidelines such as GINA, European Respiratory Society (ERS)/American Thoracic Society (ATS) and National Heart Lung and Blood Institute (NHLBI) guidelines. All trials required study participants to be a regular user of ICS treatment before enrolment into the RCT. In total, 22,173 participants were randomised in the 87 studies included in the systematic review.

2.9.2 Risk of bias in included studies

Appendix 3 shows a summary of the risk of bias for all included studies.

2.9.2.1 *Allocation*

Forty-eight studies (55.2%) were assessed as having a low risk of selection bias for the random sequence domain because the authors used computer-generated random sequence. The remaining thirty-nine (44.8%) studies were categorised as having an unclear risk of bias because, despite being described as ‘randomised', no further information was provided.

Twenty-eight (32.2%) studies were assessed as having a low risk for the allocation concealment domain, and fifty-nine (67.8%) studies were evaluated as having an unclear risk of bias in the allocation domain because no information was provided that described how allocation concealment was maintained throughout the study.

2.9.2.2 *Blinding*

Thirty-seven studies (42.5%) were judged as having a low risk of performance bias, and forty-six (52.9%) studies were evaluated as having an unclear risk of performance bias. Four studies (4.6%) were assessed as having a high risk of performance bias. Of these four, two studies (129, 191) were open-label design; one study where (149) both investigators and participants were not blinded, and, in the other study, (204) the study investigators were blinded, but no information was provided regarding blinding of study participants. Twenty-five (28.7%) studies were assessed to have a low risk of detection bias, while the remaining fifty-eight (66.7%) studies were judged as having unclear detection bias because they did not provide information regarding blinding of outcome assessors.

2.9.2.3 *Incomplete outcome data*

Most studies were assessed as having a low risk of attrition bias with only three (3.4%) studies evaluated as having an unclear risk and two (2.3%) studies were assessed as high risk. Gotfried et al. (161)reported clinical outcomes for the clarithromycin group and omitted data in the control group, rationalising that valid comparisons could not be conducted because of unequal population distribution between the two groups. Kishiyama et al. (174) enrolled 54 participants, only 30 participants completed the study, but details about patients who did not complete the study were not reported. Of the three studies assessed as unclear risk, Pavord et al.(204) did not provide information on the two out of 17 who did not complete the study ; Salmun et al. (192) omitted information on the patients who were screened and patients who withdrew from the study, while Wenzel et al. (203) did not provide reasons why patients withdrew from the study.

2.9.2.4 *Selective reporting*

Eighty-five (97.7%) studies were judged as having a low risk of selection bias. Two (2.3%) studies had a high risk of selection bias; one study (159) pre-specified PEF and spirometry as their secondary outcomes but the results were not reported while the other study (161), there was selective reporting of outcomes in the clarithromycin group and the control group outcomes were not published.

2.9.2.5 *Other bias*

There were no other potential sources of bias in any of the included studies that we are aware of, except one study (205). The processing of data and the writing of the manuscript in this study was done by the pharmaceutical company that funded the study.

2.9.3 Primary outcome: ICS and LABA combination therapy adherence reporting in the included studies

Out of the eighty-seven RCTs included (22,173 study participants), eleven assessed adherences to ICS/LABA therapy using objective methods (Table 2-1). Of these eleven, seven assessed adherence to ICS/LABA therapy in the run-in or screening phase of the study; two studies (135, 204) continuously monitored adherence throughout the course of the study, while the other two RCTs documented results either in the discussion (181) or under the methods section (132). Of the eleven studies that objectively assessed adherence, six assessed adherence using electronic diary in 5357 (24.1%) study participants. One study used FeNO to assess adherence (206) in 109 (0.5%) study participants. Another study (180) with 26 (0.12%) study participants canister weight was measured and a further three studies reviewed primary and secondary care issuing of prescription records in 86 (0.4%) study participants. Reviewing of prescription records included reviewing prescription refills in one study (132) and measurement of drug level bioassays (132, 181).

Nine studies reported that assessing adherence to ICS/LABA therapy by use of subjective methods (Table 2-2). Five studies assessed adherence in the run-in or

screening phase, while three studies assessed adherence throughout all the phases of the study and one study (207) did not assess adherence but reported that they assumed adherence would have been assessed by respiratory physicians before patients were invited to participate in the study. Five studies used the self-report method to assess adherence in 1022 (4.6%) study participants. Self-reported included a discussion about adherence during a study visit and patient's documenting adherence on a paper diary (Table 2-2). Two clinical trials (89, 133) reviewed inhaler technique in 733 (3.3%) study participants. Two studies (152, 162), reported adherence being assessed in 909 (4.1%) study participants. However, the method used to evaluate adherence was not described in these two studies.

Table 2-1 Summary of findings

Objective methods of assessing and reporting adherence to ICS/LABA therapy
FeNO: Fractional Exhaled Nitric Oxide; ICS: Inhaled Corticosteroids; LABA: long-acting beta-2 agonist

Study	Number of participants	Stage of study	Adherence reporting	Objective assessment of adherence	Inhaler technique
Nair (Benralizumab) 2017	220	Screening/Run in	Patients reported compliance with ICS/LABA daily on electronic diaries and were enrolled if they demonstrated compliance of ≥ 70%	Electronic diary	Inhaler technique was not assessed/ reported

Study	Number of participants	Stage of study	Adherence reporting	Objective assessment of adherence	Inhaler technique
Hanania (Lebrikizumab) 2016	2148	Screening	Patients recorded inhaler use daily on an electronic diary	Electronic diary	Inhaler technique was not assessed/ reported
FitzGerald (Benralizumab) 2016	1306	Run in	Daily asthma diaries were used by patients to record compliance with ICS/LABA and were enrolled if they demonstrated compliance of ≥ 70%	Electronic diary	Inhaler technique was not assessed/ reported
Bleecker (Benralizumab) 2016	1204	Run in	Daily asthma diaries were used by patients to record compliance with ICS/LABA and were enrolled if they demonstrated compliance of ≥ 70%	Electronic diary	Inhaler technique was not assessed/ reported

Study	Number of participants	Stage of study	Adherence reporting	Objective assessment of adherence	Inhaler technique
Brightling (tralokinumab) 2015	452	Throughout the study	Patients were prompted to take their required dose of ICS/LABA through a trigger in the electronic patient-reported outcome device. Patients were asked to return used inhalers to study sites to facilitate assessment of compliance	Electronic diary	Inhaler technique was not assessed/ reported
Pavord (Bronchial thermoplasty) 2007	27	Throughout the study	Patients recorded use of usual asthma medication daily on the electronic diary	Electronic diary	Inhaler technique was not assessed/ reported
Marin (Nedocromil sodium) 1996	26	Screening	Assessment of the difference between the observed canister weight and	Weighing inhaler canister	Inhaler technique was not assessed/ reported

Study	Number of participants	Stage of study	Adherence reporting	Objective assessment of adherence	Inhaler technique
			the expected weight		
Hodgson (Ciclesonide) 2015	30	Screening	Assessment of primary and secondary care prescribing information	Review of prescription records	Inhaler technique was not assessed/ reported
Brusselle (Azithromycin) 2013	109	Run in	Inhaler technique was reviewed and optimised before enrolment. Patients were only included if a FeNO level was <50 parts per billion to ensure adherence to ICS	FeNO	Inhaler technique was assessed/ reported
Morjaria (Etanercept) 2008	26	Documentation of adherence monitoring was reported under methods section	General practitioner prescription records were reviewed bioassay for serum theophylline levels were collected	Review of prescription records	Inhaler technique was not assessed/ reported

Study	Number of participants	Stage of study	Adherence reporting	Objective assessment of adherence	Inhaler technique
Berry (Etanercept) 2006	30	Documentation of adherence monitoring was reported under methods section	Primary care records on the issuing and filling of prescriptions were reviewed. Pharmacists consulted patients at their homes. Measurement of serum prednisolone, cortisol, and theophylline concentration	Bioassays and review of primary care records on the issuing and filling of prescriptions	Inhaler technique was not assessed/ reported

Table 2-2 Summary of findings

Subjective methods of assessing adherence to ICS/LABA therapy

Study	Number of participants	Stage of study	Adherence reporting	Methods of monitoring adherence
Hanania (Lebrikizumab) 2015	463	Screening	Patients who reported good adherence to background controller medication were randomised	Self-report
Cahill (Imatinib)2017	62	Throughout the study	Patients used a diary to record their inhaler use	Self-report
Piper (Tralokinumab) 2013	194	Throughout the study	Investigators discussed with patients about use of controller medication at each study	Self-report
Corren (Lebrikizumab)2011	218	Run-in	Response from author	Self-report
Tamaoki Th2 antagonist (IL4/IL5 inhibitor)2000	85	Throughout the study	Daily recording of all the medications taken throughout the study in a booklet	Self-report
Bjermer (Reslizumab) 2016	314	Screening	Patients were asked to report compliance with ICS/LABA therapy and were asked	Inhaler technique

Study	Number of participants	Stage of study	Adherence reporting	Methods of monitoring adherence
			to demonstrate inhaler technique	
Humbert Omalizumab 2005	419	Run-in and screening	During the run-in period, inhaler technique was assessed.	Inhaler technique
Hanania (Omalizumab) 2011	850	Throughout the study	Adherence to ICS and LABA was assessed at clinic visits during run-in and treatment phase	Not documented
Dente (Prednisolone) 2010	59	Screening	Compliance with treatment assessed when determining eligibility	Not documented

2.9.4 SECONDARY OUTCOMES:

The large high level of heterogeneity between the studies with regards to treatment interventions, treatment dosage and inconsistencies in the units of the reported outcomes (for example the mean percentage change in FEV1 or absolute values were reported) meant that only limited meta-analyses could be performed. Meta-analysis was conducted to compare the thirteen studies that assessed adherence to ICS/LABA therapy with objective methods with studies that did not assess adherence including studies that evaluated adherence using subjective methods. The conducted meta-analyses were limited to studies that conducted trials of biologic therapy against a placebo if data were available. Where dosing regimens were used in the same study, these studies were included as four different studies in the meta-analyses because a composite result combining the results for the four different doses was absent, for example, Hannania et al.(163)

Lebrikizumab LAVOLTA 1 and 2 studies (Figure 2.1, Appendix 4). Pre-bronchodilator FEV1 and morning PEF were used for the analyses.

2.9.4.1 *Effects of treatment compared to placebo in studies that report adherence to ICS/LABA therapy and those studies that do not report adherence*

2.9.4.1.1 Forced expiratory volume in one second (FEV1)

The weighted mean difference in FEV1 between the active-add-on treatment and the placebo add-on therapy for trials that reported adherence to ICS/LABA therapy was significant at 0.09 litres (95% CI: 0.06, 0.11), (Figure 2.1 , Appendix 4) but was not significant for studies that did not report adherence, mean difference 0.11 litres (95%CI: -0.10, 0.32) (Figure 2.2, Appendix 4). The studies that reported adherence were homogenous (I^2= 0%) while there was a significantly high level of heterogeneity across the studies that didn't report adherence (I^2 = 98%).

2.9.4.1.2 Peak Expiratory Flow Rate (PEF)

There was also a statistically significant weighted mean difference in PEF between the active-add-on therapy and the placebo add-on for studies that reported adherence {8.48 L/min (95% CI: 2.41, 14.56)} (Figure 3.1, Appendix 4), these studies were homogeneous (I^2=29%). The pooled mean difference in PEF for the studies that did not report adherence was statistically significant; 33.52L/min (95%CI: 30.30, 36.74) (Figure 3.2, Appendix 4), these had a non-significant moderate level of variability (I^2= 53%).

2.9.4.1.3 Asthma Quality of Life (AQLQ)

The weighted mean difference AQLQ between the active-add-on therapy and the placebo add-on for studies that reported adherence was 0.12 (95% CI: 0.01, 0.24) (Figure 4.1, Appendix 4) and 0.51 (95%CI: -0.59, 1.61) for studies that did not report adherence (Figure 4.2). There was a significant moderate level of variability across the studies that reported adherence (I^2 = 57%, p=0.01) and a significantly high degree of variability across the studies that did not report adherence (I^2 = 99%, p<0.00001).

2.9.4.1.4 Asthma Control Questionnaire (ACQ)

The weighted mean difference ACQ between the active-add-on therapy and the placebo add-on for trials that reported adherence was not statistically significant -0.06 (95% CI: -0.14, 0.02) (Figure 5.1, Appendix 4). The mean pooled difference in ACQ for the studies that did not report adherence was statistically significant -0.43 (95% CI: -0.44, -0.42), (Figure 5.2, Appendix 4). The studies that reported adherence were homogenous (I^2= 0%) while there was a high level of heterogeneity across the studies that didn't report adherence (I^2 = 75%).

2.9.4.2 *Assessment of the placebo effect*

2.9.4.2.1 FEV1

The weighted mean difference in FEV1 from baseline to the end of the study for the included studies was not statistically significant 0.10 litres (95% CI: -0.03, 0.23), (Figure 6, Appendix 4). There was a high level of heterogeneity across the included studies (I^2 = 89%).

2.9.4.2.2 PEF

The weighted mean difference in PEF from baseline to the end of the study for studies that reported adherence was not statistically significant 3.20 litres/minute (95% CI: -4.74, 11.14) (Figure 7, Appendix 4). All the studies were homogeneous (I^2=0).

2.9.4.2.3 AQLQ

There was a statistically significant weighted mean difference in AQLQ from baseline to the end of the study which was 0.48 (95% CI: 0.28, 0.68), (Figure 8, Appendix 4). Two studies reported adherence to ICS/LABA therapy, Bjemer et al. (133) and Hodgson et al. (165) and 10 trials (149, 151, 161, 167, 173, 189, 191, 208-211) did not report adherence to ICS/LABA therapy. High level of heterogeneity (I^2= 85%) exists amongst the studies.

2.9.4.2.4 ACQ

There was a statistically significant difference in mean ACQ from baseline to the end of the study for studies all the studies that did not report adherence was -0.57

(95% CI: -0.63, -0.51), (Figure 9, Appendix 4). There was a high level of heterogeneity across all the studies (I^2=82%).

2.9.4.3 *Estimating the effects of assessing adherence to ICS/LABA therapy on clinical outcomes*

Adjusting the standard deviations for the assessment of adherence during the run-in or screening phase screening phase as well as throughout all the phases of the study, the pooled mean difference in FEV1 was 0.07 (95% CI: 0.00,0.13) compared with 0.02 (95% CI: -0.09,0.13) (Figures 10.1 and 10.3 respectively, Appendix 4). Similarly, adjusting the standard deviations for assessment of adherence during the run-in or screening phase as well as throughout all the phases of the study resulted in a pooled mean difference of PEF was 13.74 (95% CI: 10.06, 17.43), compared with 10.66 (95% CI:5.94, 15.39) (Figures 11.1 and 11.3 respectively). Adjusting the standard deviations for assessment of adherence during the run-in or screening phase of the study the pooled mean difference in PEF was 11.43 (95% CI: 4.23, 18.62), compared with 10.66 (95% CI: 5.94, 15.39) (Figures 11.1 and 11.2).

2.9.4.4 *Estimating sample size and study power*

The standard deviations for the change in FEV1 from baseline ranged from 0.31 to 0.55 (Figure 10.1, Appendix 4). Assuming an effect size of 0.10 and equal sample size allocated to the active add-on therapy and placebo add-on therapy I plotted the power graph (Figure 12, Appendix 4). The assessment of adherence at baseline as well as throughout the conduct of the study leads to an increased study power of approximately 85% (Figure 12). Assuming an expected effect size of 0.10 and an equal SD for both the active add-on group and the placebo add-on group, I plotted a sample size graph (Figure 13). The sample size was reduced from approximately 420 to 180 when adherence was assessed at baseline and throughout the conduct of the clinical trial.

2.10 DISCUSSION

The review indicates that assessment of adherence to ICS/LABA therapy in clinical trials is infrequently done. Distinguishing difficult to treat asthma from 'refractory'

asthma during the run-in phase or screening phase is critical to ensure enrolled patients are eligible for the treatments in compliance with established guidelines for treatment of asthma. Failing to assess adherence to maintenance asthma therapy during the screening or run-in period leads to recruitment of patients who are not suitable for step-up treatment. Non-informative data may be introduced into the study, and, subsequently, there is a reduction of the effect size by the proportion of non-informative subjects included in the study, (122) thereby underestimating the actual effect size. Therefore, a larger sample size will be required to overcome the effects of the non-informative patients. It will be cost-effective to exclude participants with non-informative data rather than trying to overcome the impact of non-informative data by increasing sample size (212).

2.10.1.1 *Summary of main results*

I identified 87 randomised, placebo-controlled, clinical trials involving 22,174 patients with severe uncontrolled asthma despite ICS therapy or a combination of ICS and LABA therapy as maintenance treatment for asthma. The study duration ranged from 2 to 52 weeks. Most studies were at low or unclear risk of selection bias, detection bias and biases associated with blinding. As suggested by the GINA asthma management document, adherence to the currently prescribed ICS/LABA therapy before adding therapy was reported to have been performed in twenty trials involving 8,242 (37.2%) patients. Eleven trials (n= 5578, 25.1%) assessed adherence to ICS/LABA therapy using objective methods. However, there were variations in measures of adherence used including FeNO, electronic diary, weighing inhaler canister, review of primary and secondary care issuing of prescription records. Nine studies (n=2664, 12%) used subjective methods. The subjective techniques used to assess adherence of self-report are notoriously unreliable making it difficult to distinguish the impact of subjectively evaluating adherence versus objectively assessing adherence on clinical outcomes. Despite the GINA recommendation that inhaler technique be checked as part of routine asthma care, inhaler technique was reported to have been checked in three studies involving 842 patients (3.8%).

Despite a large number of included studies, the high levels of heterogeneity across studies concerning different drug interventions, differences in outcome measures, as well as inconsistency in reporting and defining outcomes such as exacerbations, meant that detailed meta-analyses often could not be conducted. It was possible to evaluate the difference in outcomes in studies when adherence to ICS/LABA was and were not reported to have been assessed (122). In this meta-analysis, a statistically significant mean difference was found in FEV1 for both studies that reported adherence to ICS/LABA therapy {0.09 litres (95% CI: 0.06, 0.11)} and the studies that did not report adherence to ICS/LABA therapy {0.12 litres (95%CI: 0.07, 0.17)}. However, there was a high level of heterogeneity (I^2=98%) in the FEV1 for the studies that didn't report adherence. There was a statistically significant mean difference in both PEF studies that reported adherence and for the studies that did not report adherence, but the pooled mean difference in AQLQ was only significant for the studies that reported adherence to ICS/LABA therapy. The mean difference in ACQ for the studies that reported adherence to ICS/LABA therapy and those that did not report adherence was not statistically significant. Despite the heterogeneity in the included trials, the assessment and reporting of adherence to maintenance asthma therapy resulted in statistically significant between-group differences in the study outcomes.

A placebo effect is usually expected to occur in clinical trials and may affect the effectiveness of the treatment, thus effectively influencing the study outcome results (213). In this systematic review, there was a clinically important and statistically significant placebo-effect for both AQLQ {0.48 (95% CI: 0.28, 0.68)} and ACQ {-0.57 (95% CI: -0.63, -0.51)}. A placebo effect was observed for PEF and FEV1, but it was not statistically significant since the confidence intervals included no difference. This is consistent with results of previous studies (120) confirming that the placebo response influences improvement of subjective outcomes. Accounting for the placebo effect during data analysis ensures the reliability of the data.

In the model of the effect of the absence of assessing adherence at baseline and throughout the conduct of the clinical trial, I have shown that a significant amount

of variance exists if adherence to standard therapy (ICS/LABA) is not assessed during the run-in phase and throughout the conduct of the RCT. If adherence is not monitored, then the variances and the corresponding standard deviations become higher than they should be. Adjusting the standard deviations for the assessment of adherence during the run-in and throughout all the phases of the study, the pooled mean difference FEV1 improved from 0.02 (95% CI: -0.09, 0.13) to 0.07 (95% CI: 0.00, 0.13).

Similarly, adjusting the standard deviations for assessment of adherence during the run-in and throughout all the phases of the study resulted in an improvement in the pooled mean difference in PEF from 10.66 (95% CI: -5.94, 15.39) to 13.74 (95% CI: 10.06, 17.43). Consequently, the study power can be significantly increased, and the sample size decreased. Inadequate assessment of adherence to ICS/LABA therapy in the screening/run-in phase and failure to continuously monitor adherence to maintenance therapy in the trials of add-on treatment can incur significant extra costs because larger sample sizes will be required to overcome the contribution of variance resulting from not assessing adherence.

In clinical trials of add-on therapy, the assessment of outcomes such as exacerbations is based on pre-determined exacerbation usually a year before enrolment. Heaney et al. have shown that exacerbations rates are higher in poorly adherent patients (214).This means that the patients with ‘‘difficult to control’ asthma’ rather than ‘refractory’ asthma will be recruited into these clinical trials. The enrolment of patients who are not eligible for add-on therapy will introduce a higher placebo effect into the subjective outcomes such as exacerbation. This high placebo effect has been prevalent in the clinical trials of anti-IL5 therapy assessing exacerbation rates/and or steroid reduction rates (100, 118, 134, 155, 215, 216). Therefore, the substantial placebo effect can be reduced by assessing adherence during the conduct of clinical trials.

Incorporating objective measures of adherence to the methodology of conducting clinical trials will be considered best practice, and in compliance with national and

international guidelines. Unfortunately, management of severe asthma is far from optimal care because of non-compliance with guidelines as evidenced by the results of this review.

Unfortunately, the guidelines do not offer standardised measures of assessing adherence. Most of the available methods of assessing adherence are inadequate. They neither review inhaler technique nor assess the inhaler timing of use. The available methods of assessing adherence include: diaries which require patients' adherence to both medication and record keeping and have been found to overestimate adherence (217); electronic monitors, which have the advantage of assessing the frequency of inhaler use but do not assess inhaler technique and the timing of inhaler use; and weighing and inhaler dose counting are both affected by dose (218). Monitoring drug levels offer another alternative but are invasive, expensive and time-consuming and can be hindered by drug and food interactions (219, 220). To overcome the limitations of methods used to assess adherence to inhaled medical therapy in asthma, it is crucial to develop validated objective methods that evaluate the timing of inhaler use as well as inhaler technique. Delivering personalised education on inhaler adherence will also be critical in addressing non-adherence.

2.10.1.2 *Strengths and limitations*

To my knowledge, this is the first systematic review examining ICS/LABA treatment adherence in clinical trials of additional therapy to maintenance treatment in severe asthma. The strengths of this review include the comprehensive literature searches, appraisal and reporting of the risk of bias and the evidence-based inferences.

Some factors should be considered when interpreting this review. This review included studies published from 1995 to 2017, and, hence, the outcomes that were chosen to be assessed in the study, sample size calculations and the guidelines of reporting RCTs, would have changed in that time frame. This resulted in limited information being available to conduct further meta-analyses. The quality of the

available data also limits the review. There is significant heterogeneity across the studies; therefore, interpretation of the meta-analysis with regards to the between group differences in outcomes should be guarded. The heterogeneity across the studies included different therapies (such as monoclonal antibodies, bronchial thermoplasty, macrolide antibiotics, anti-tumor necrosis factor and oral corticosteroids); different sample sizes and variety in the duration of the studies which ranged from two to fifty-two weeks. There were inconsistencies in reporting outcomes such as exacerbations. The definitions of exacerbation varied across clinical trials and the inconsistency of reporting an exacerbation across clinical trials made it difficult to conduct a meaningful comparison.

2.11 CONCLUSION

The results of this study indicate that relatively few studies assessed adherence to ICS/LABA therapy prior to randomisation or monitored adherence to this therapy during the conduct of the clinical trials. Among those that did assess adherence, the methods used were semi-objective or subjective methods. It is crucial to use adequate methods of measuring adherence in clinical trials so that clinicians can confidently make clinical decisions to manage severe asthma based on the results of clinical trials. Incorporating objective inhaler adherence monitoring in the conduct of clinical trials would be cost-effective, less time consuming and will ensure good quality data.

In chapter 3, I will explore the use of an objective method of measuring adherence, INCA device, in assessing adherence to ICS/LABA therapy in severe uncontrolled asthmatics. The adherence data from the INCA device will be incorporated into patients' symptoms and lung function to aid a clinician to make decisions about escalating or decreasing asthma therapy.

Chapter 3. Designing a prospective randomised multicentre trial of the effect of providing feedback on inhaler technique and adherence from an electronic device to optimise the management of symptomatic uncontrolled asthma patients

3.1 INTRODUCTION TO THE CHAPTER

At a population level, treatment with inhaled corticosteroids (ICS) with the addition of LABA is highly effective in controlling symptoms and preventing exacerbations of asthma. However, at an individual level treatment is affected by different factors such as poor adherence, different underlying mechanisms and phenotypes of asthma. Patients with 'refractory' asthma respond to ICS therapy in different ways, some being resistant to ICS therapy. In clinical practice, it can be difficult to distinguish patients with poor adherence ('difficult to control') from patients with 'refractory' asthma because the few available objective measures of inhaler adherence are unreliable. In chapter 2, I have shown that assessment of inhaler adherence in clinical practice and clinical trials is limited by the inadequacy of the available methods of assessing adherence. These methods are inadequate because they don't assess the inhaler technique and the timing of inhaler use. To address the limitations of some of the current methods of assessing inhaler adherence such as electronic diaries, review of prescriptions and dispensing records, there have been development of electronic monitors that have the advantage of assessing the timing of inhaler use and inhaler technique. The INhaler Compliance Assessment (INCA) technology is one of these electronic devices which assesses inhaler adherence by establishing when and how well an individual has used the inhaler. This method of measuring adherence has been shown by the INCA group to be more reflective of changes in clinical outcomes than the current methods of measuring adherence in patients with asthma and COPD (82, 221). In this chapter, I describe the design of a prospective randomised, multicentre study of patients with severe uncontrolled asthma comparing two educational interventions that I led, with final data collection still ongoing.

3.2 BACKGROUND

Asthma is a heterogeneous chronic inflammatory disease of the airways, which is characterised by symptoms such as a cough, breathlessness, and wheeze, as well as airflow obstruction, and airway hyper-responsiveness. Frequent exacerbations requiring oral corticosteroids are a predominant feature in patients with severe

asthma. Such patients have high rates of health care utilisation and loss of productivity, the two primary drivers in asthma cost (55). Before escalating therapy, effective treatment of patients with severe asthma includes confirming the diagnosis, treating comorbidities and assessing and addressing adherence to inhaled therapy, including correcting inhaler technique (2, 4). The challenge in implementing this strategy is that it may be difficult for clinicians to distinguish patients with 'difficult to control' asthma from those with 'refractory' disease. This is because patients with 'difficult to control' asthma and patient's with 'refractory' asthma are commonly characterised as having severe asthma. European Respiratory Society (ERS)/ American Thoracic Society (ATS) guidelines suggest that when a diagnosis of asthma is confirmed and comorbidities have been addressed, severe asthma should be defined as; asthma which requires treatment with high dose ICS (adult fluticasone propionate dose of ≥1000mcg and budesonide dose of ≥ 1000mcg) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy (222). Therefore, a clear distinction between severe asthma and difficult-to-control asthma is necessary.

Difficult-to-control asthma denotes to the extent to which the manifestations of asthma have not been reduced or removed by treatment (223). Difficult-to control can arise due to multiple factors such as: persistently poor compliance; psychosocial factors, dysfunctional breathing, vocal cord dysfunction; persistent environmental exposure to allergens or toxic substances; and untreated or undertreated comorbidities such as chronic rhinosinusitis, reflux disease or obstructive sleep apnoea syndrome. However, asthma severity is determined by the asthma phenotype which may be characterised by pathological and physiological markers. Three clinical phenotypes of severe 'refractory' asthma have been described: exacerbation prone asthma (patients suffer from frequent severe exacerbations with relatively stable episodes between exacerbations); asthma with fixed airflow obstruction; and steroid-dependent asthma *(*patients depend on systemic corticosteroids for daily control of their asthma) (224). Two pathological phenotypes of severe 'refractory' asthma have been described; eosinophilic and

non-eosinophilic asthma. Severe asthma with persistent eosinophilia is characterised by mixed eosinophilia and neutrophilia in bronchial biopsies and induced sputum despite the use of high-intensity ICS or oral corticosteroid treatment. It has been associated with severe exacerbations (225), sinus disease (226), airway remodelling (91),and fixed airflow obstruction (227),and patients are likely to respond targeted Th2- therapy such as anti-IgE and anti-IL5 (183, 228). Non-eosinophilic severe 'refractory' asthma is characterised by airway neutrophilia (229), and the eosinophils are either absent or suppressed (230). Therefore, distinguishing difficult-to-treat asthma from severe 'refractory' asthma allows accurate characterisation of patients with 'refractory' asthma who will benefit from targeted phenotype specific biologic therapy. Furthermore, the causes of difficult-to-treat asthma such as poor adherence can be identified and addressed.

To identify optimal inhaler adherence, clinicians must assess that an individual is taking the inhaler with proper technique and taking the correct dose at the correct time. As previously mentioned in chapter 1 and chapter 2, there are several available methods that are used to measure inhaler adherence such as patient diaries, pharmacy refill records and weighing of inhaler canister. These methods are inadequate in assessing inhaler adherence because they neither assess the time the inhaler was used nor assess inhaler technique. Furthermore, the methods of assessing inhaler technique do not offer patients individualised feedback on inhaler technique and most healthcare professionals are unfamiliar with the correct inhaler technique. New developments in research have led to invention of electronic devices such as the propeller health and Inhaler Compliance Assessment (INCA) device. The propeller health attaches to the MDI inhaler and monitors inhaler use by recording the date, time, and number of inhaler use (78).The information is conveyed to a Bluetooth paired smartphone, which records the location of the event and securely uploads these data to remote servers. When used to monitor short acting beta-2 agonist (SABA) use in a study of asthma patients over a 12 month period, the patients who received feedback from the propeller health had a reduction in SABA use and there was a significant improvement in the proportion of

ACT score in patients who had uncontrolled ACT scores at baseline (78). The INCA device attaches to a Diskus inhaler and the microchip in the device electronically records when and how well the inhaler is used. The audio files are downloaded from the device onto a webserver and the audio files can be analysed to provide information on inhaler technique errors such as exhalation after drug priming, multiple actuations and multiple inhalations. The unique characteristics of the audio of inhalation have been thoroughly studied, validated automated algorithms have been developed (231-243), and validation of the INCA technology against other measures of adherence has been performed (244). The analysis of the digital audio recordings from the INCA device allows an objective assessment of a patient's inhaler adherence. Thus, both patients' habit of inhaler use and inhaler technique is assessed, and hence patient-tailored adherence interventions could be implemented by clinicians.

Recent data using inflammatory biomarkers have confirmed that poor asthma control may arise because of the disease heterogeneity. Data from these studies (105, 106, 245, 246) have shown that non-eosinophilic asthma (Type-2 -Low) account for 50% of patients with symptomatic asthma. These patients demonstrate a minimal response to steroid therapy. Understanding the underlying asthma inflammatory phenotype enables identification of differential responses to ICS in patients with 'refractory' asthma which is critical for targeted biologic therapy. This was demonstrated by earlier Mepolizumab studies (156, 247) which failed to demonstrate significant reduction in asthma exacerbations which may be due to lack of identification of a subgroup of patients with eosinophilic exacerbations who were likely to respond to this therapy. However, the development of disease biomarkers such as high periostin levels targeted by Dupilumab (101, 102); IgE targeted by omalizumab (89, 248) and high eosinophil levels targeted by anti-IL5 biologic such as Mepolizumab(95, 96, 249) has resulted in treatment efficacy in reduction of exacerbations. Therefore, in severe 'refractory' asthma, an understanding of both the underlying pathophysiologic mechanisms driving airway inflammation and the identification of appropriate biomarkers in individual patients

(250) are critical in guiding the use of biologics and monoclonal antibodies that target the specific pathological processes. This means that the interpretation of the patient's inflammatory phenotype, identifying and addressing poor adherence are essential in the assessment of severe uncontrolled asthma patient in the context of widely available expensive biologic therapy.

In this chapter, I describe the design of a study of patients with severe, uncontrolled asthma attending specialist hospital asthma clinics in the Republic of Ireland and Northern Ireland. The study compares two education interventions on inhaler adherence education. The INCA device is used to monitor fluticasone/sameterol and salbutamol inhaler use. The active group will receive INCA feedback education on their use of salmeterol/fluticasone and beta agonist reliever use and electronic PEFR data, while the control group will receive guideline-recommended asthma education and clinical monitoring. The study had two phases. The first phase involved a nurse-led asthma training and inhaler education to improve adherence. In the second phase of the study, a clinician adjusted medication during the study visits. The protocol, physician script and recruitment, the study procedures are described.

3.3 PROTOCOL DEVELOPMENT

The study protocol had been initially developed in 2013 and hence I spent the first three months of the project revising the study protocol and applying for ethics approval from multiple sites. I was involved in the study design, protocol development, designing the physician script for the study, recruitment of the study participants, training of the doctors and nurses involved in the study at different study sites. I actively recruited 130 patients and completed study investigations in 90 patients from start to finish of the study. I was also involved in data collection (including all study related procedures such as performing spirometry, FeNO, blood tests, and conducting nursing/ physician visits) and interpretation. I also reviewed the 90 patients in the clinic post completion of the study.

3.3.1 HYPOTHESIS

I hypothesised that digitally recorded inhaler adherence, and PEFR information would be advantageous if used by clinicians to either identify patients with 'refractory' asthma and hence escalate treatment to biologic therapy or identify patients with 'difficult to treat' asthma who need to work on their adherence with a possibility of stepping down their therapy (for example reducing down the salmeterol/fluticasone dose from 50/500mcg to 50/250mcg).

3.3.2 STUDY OBJECTIVE

The purpose of this study was to use objectively measured adherence from the INCA device and PEFR to direct clinical decisions when using the GINA-recommended cycle of review and medication change. I also assessed whether feedback to the patient on their inhaler adherence using the INCA and aligning this information to electronically recorded PEFR data would lead to persistence of adherence over the eight-month period.

3.3.3 PRIMARY OUTCOMES

The study has two co-primary outcomes:

1. To assess if a clinician's knowledge of objectively measured adherence and PEFR influences medication prescription step-up therapy (such as a monoclonal antibody). In other words, to see if adherence is incorporated into guideline directed clinical decision making. This will be assessed by comparing the proportion of patients with 'inappropriate' asthma medication prescriptions in the control group versus the active group and assessing the overall cost of these medication prescriptions at the end of the study.
2. To assess if giving feedback to the patient on their adherence using the INCA device and aligning this information to electronically recorded PEFR data

leads to a higher rate of long-term adherence, assessed over the last 12 weeks of the study, compared to usual care.

3.3.4 SECONDARY OUTCOMES

The secondary outcomes are listed below.

3.3.4.1 *Patient-reported outcomes*

- To compare the Asthma Control Test (ACT), Asthma Quality of Life Questionnaire (AQLQ) scores, EQ-5D-3L scores, Work Productivity and Activity Impairment-Asthma (WPAI-Asthma) scores and PEFR rates between the active and control groups.

3.3.4.2 *Clinical outcomes*

- To examine and compare the proportion of patients reaching stated clinical goals.
- To compare the proportion of patients who are 'refractory', defined as having actual adherence ≥80%, ≥1 exacerbation, PEFR am/pm <80% and ACT ≤19.
- To compare the proportion of patients who are non-adherent and remain uncontrolled, i.e. Actual Adherence <80%, PEFR am/pm <80% and ACT ≤19.
- To compare the time to first exacerbation (defined by ≥20% fall in PEFR and at least doubling of reliever use for three consecutive days or prescribed rescue oral steroid) between the active and control groups.
- To compare the proportion of patients with inhaler related side effects including oral candidiasis between the active and control groups.
- To compare changes in blood eosinophils, periostin and Fractional Exhaled Nitric Oxide (FeNO) between the active and control groups.
- To investigate the relationship between biomarker changes with adherence.
- To compare the proportion of patients who were clinically stable (i.e. the proportion of patients who required no daily reliever use in the month before study end) between the active and control groups.
- To investigate the relationship between changes in FeNO (characterised into FeNo >45ppb or FeNO <45ppb) and adherence.

- To investigate the relationship between 7-day FeNO suppression and clinical and biomarker outcomes.

3.3.4.3 *Economic outcomes*

- A cost-effectiveness and cost-utility analysis of the INCA educational intervention compared to the control arm will be performed. Also, an economic evaluation of the national implementation of the INCA-SUN program will be conducted (budget impact analysis).
- To compare the average time lost to work between the active and control groups.

3.3.5 PARTICIPATING CENTRES, ETHICS AND RECRUITMENT PLAN

Patients were recruited from 5 hospital centres in the Republic of Ireland and Northern Ireland. The hospitals chosen were Beaumont Hospital, St Vincent's Hospital, Cork University Hospital, James Connolly Memorial Hospital and Belfast City Hospital. Failure to recruit was a threat to the study and therefore, a contingency plan was to consider recruitment from sites such as Tallaght University hospital, Mater Misericordiae University hospital and Galway University hospitals if there was failure to recruit 20- 30 patients at each participating site. After obtaining ethics approval for the principal site (Beaumont Hospital), I submitted ethics applications for the other five participating centres (James Connolly Memorial Hospital, Cork University Hospital, Tallaght University Hospital, St Vincent's University Hospital) in Ireland prior to the screening phase of the study. The Ethics application proposal for Belfast City Hospital was done by the principal investigator and the study nurse. This meant that recruitment could not at each individual site until the ethics application had been approved. Patient recruitment commenced on receipt of ethical approval at each participating site. Recruitment started in Beaumont Hospital in November 2015 and the second site started recruiting one year later (November 2016). Recruitment could not commence in Tallaght University Hospital because of lack of staff to conduct the study.

3.3.6 DETAILS OF TRIAL TEAM

3.3.6.1 *Team Organisation and Monitoring procedures*

The coordinating centre for the trial was Beaumont hospital and was staffed by the author, as the study doctor and two study nurses. I was involved in providing study interventions/education and conducting the study visits. This involved visiting multiple sites and providing hands-on training during initiation visits. The study nurse and I attended the entire initial nurse and doctor study visits at all the participating sites. The study teams from all the participating sites were invited to come and observe the study visits in Beaumont hospital prior to conducting study visits. A data manager/research assistant whose job was to monitor data and ensure data validity and the information and software manager (maintains functioning webserver and electronic CRF) were also part of the study team. The study nurse and the research assistant were responsible for the distribution of trial supplies. The trial monitoring committee comprised of five principal investigators from each participating site, the local director of clinical research and a local quality, safety and regulatory officer. A safety and regulatory officer carried out monitoring visits to each site on at least one occasion. Her job was to ensure that the study was conducted according to GCP (good clinical practice) guidelines, ensure that the protocol has been adhered to, that all pertinent information has been recorded, perform source data verification, monitor product accountability and ensure that all CRFs are complete and signed off by the investigator.

3.3.7 Data collection, safety and confidentiality

Data was collected on paper case record forms (CRFs) that I designed with the study nurse prior to patient recruitment. Paper CRFs were created for the study visit 1 to 6 and were later transcribed into electronic CRF by an information technologist in close collaboration with the author. The patient's name was retained only on the consent forms kept on patient tracking logs kept at the hospital. At all times during the data collection process, patient confidentiality was maintained by assigning a code number to each patient, which was the patient identifier on CRFs, diaries and QOL questionnaires. Data from patients at each site was retrospectively transferred to a secure electronic CRF in March 2018 once the electronic CRF was completed.

Study visits could be done electronically without the use of paper CRFs. Access to the web based electronic CRF and database was granted to the nurse and study doctor at all sites and was individualised with a username and password. Each authorised user had access to view only data related to patients from that users' site and was not able to access data relating to patients from other sites. Users' access to patient data was restricted to allow Add, Modify or Read-Only access to patient data. The tool had an inbuilt audit trail that records and can display, details of additions or changes made to data, either by user or by patient basis.

3.3.8 Safety reporting

Safety testing and a comprehensive risk assessment had been conducted to minimise potential hazards associated with the clinical investigation of the INCA device. The INCA device was securely fixed to the outer casing of the Diskus inhaler. It did not interfere in any way with the mechanism of drug delivery of the inhaler. However, in the event of any safety issues arising adverse events and serious adverse events were recorded in the case record form (CRF) and evaluated by the principal investigator. Device related adverse events were collected and reported to the manufacturer of the device and the sponsor. For example, some of the device related errors included the device not able to record while the patient was taking the inhaler, or the device recorded corrupt files that could not be analysed by the algorithm. An adverse device effect was defined as any untoward and unintended response to a medical device that occurs during the study. This included: any event resulting from insufficiencies or inadequacies of the instructions for use or the deployment of the device; any event that is the result of a user error; any untoward medical occurrence in a subject.

Safety monitoring was conducted throughout the trial with reporting of adverse event (AE) and serious adverse event (SAE) in each participant's CRF. All AEs/SAEs were reported immediately to the study PI and attending physician. An AE was defined as any unfavourable and unintended sign including an abnormal laboratory finding (such as elevated eosinophils of a low haemoglobin), symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during

the course of the study. All the asthma exacerbations reported by the patient were recorded as adverse events during the study. A SAE was defined as any untoward medical occurrence that results in: death; is life threatening; requires inpatient hospitalization or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; a congenital anomaly/birth defect. Asthma exacerbation that resulted in a hospital admission, and hospital admissions due to any illness except planned elective surgery were recorded as serious adverse events. The Sponsor was informed of SAE's within 24 hours of the investigators being aware of the SAE and the Ethics committee was informed of the SAEs during the planned annual reports.

All patient related adverse events were recorded on the adverse events page in the CRF. The information recorded included: the start and End Date or Ongoing of the adverse event; severity of event (mild, moderate or severe); relationship to device (yes / no/unknown); serious adverse event (yes/no). Each event was recorded separately, for example an adverse event such an asthma exacerbation that resulted in serious adverse event was recorded as both an adverse event and a serious adverse event. Causality was determined by the investigator. The principal investigator or the author completed, signed and dated the SAE pages on the CRF, checking that the data were consistent and accurate. The summary reports of medical adverse events were sent annually to ethics committees.

3.3.9 METHODS

3.3.9.1 *Study design and Setting*

The study is a 32-week multicentre, parallel group, prospective randomised controlled study, conducted at the clinical research centres of five university hospitals in the Republic of Ireland and Northern Ireland. The study started recruiting in October 2015 and it is still recruiting. The study consisted of two phases (**Error! Reference source not found.**). In the first phase of the study (8 weeks) the study nurse provided asthma training and inhaler education to improve adherence to salmeterol/fluticasone inhaler. The second phase (subsequent 28 weeks) of the study involved medication adjustment by a clinician. The Health

Research Board of Ireland (grant number: HRA-D1-2014-683, grant code: HRB DI 59) and GlaxoSmithKline funded the study. The hospital ethics committees of the recruiting sites (Beaumont Hospital, James Connolly Memorial Hospital, Cork University Hospital, St Vincent's University Hospital and Belfast City Hospital) and approved the study. The study was registered on Clinicaltrials.gov (NCT02307669) and the protocol for the study has been published (251).

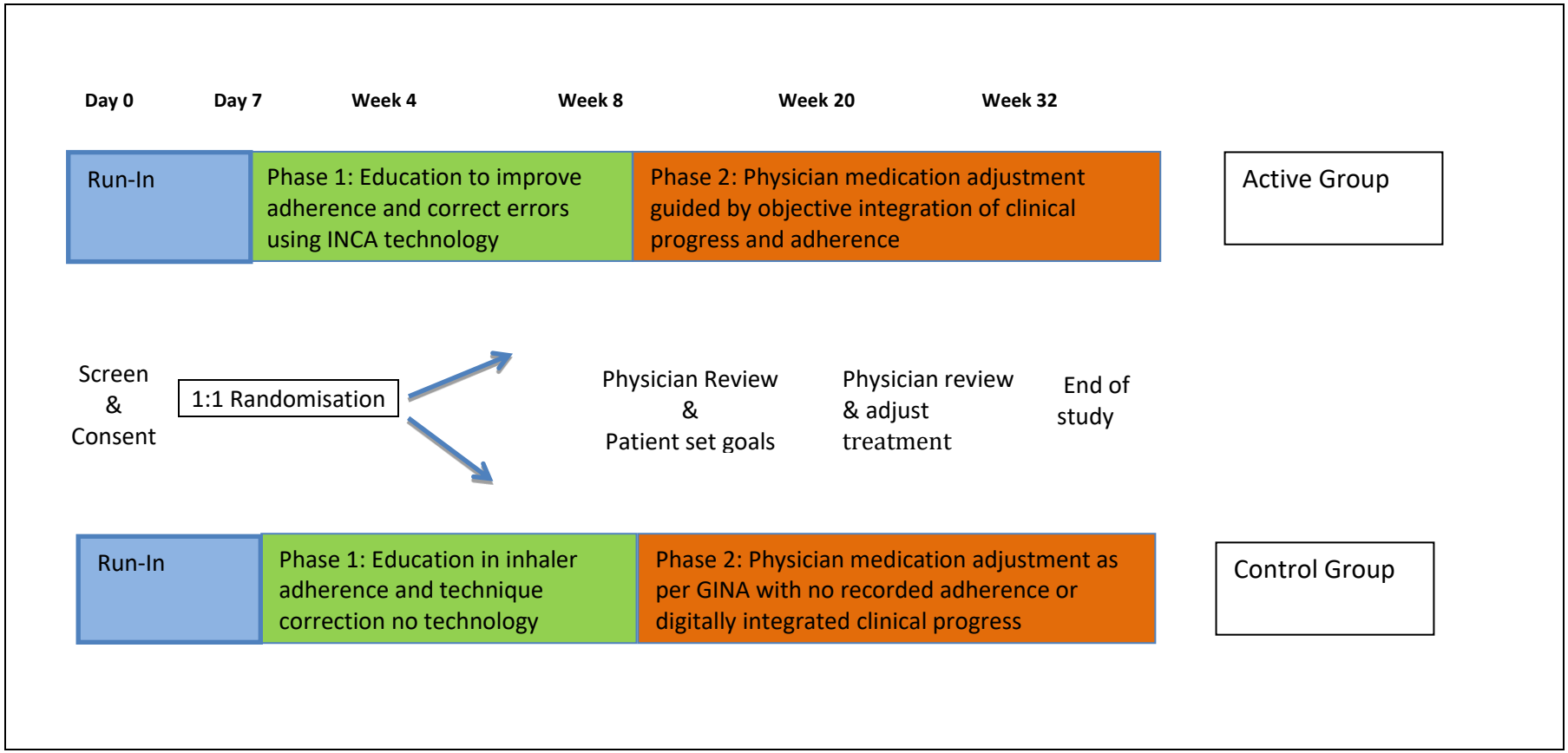


Figure 3-1 The study design

Patients with uncontrolled asthma (ACT ≤19), on asthma therapy consistent with Stage 3 to 5 of the GINA guidelines and had at least one course of oral corticosteroids (OCS) in the previous year were enrolled into the study. Patients underwent a 7-day run-in period of fractionated exhaled nitric oxide (FeNO) suppression test and were randomised in a 1:1 ratio to either the active or control group. During the first phase of the study, the patient was provided with inhaler education and the patient set goals that they wanted to achieve during the study. During the second phase of the study, the physician reviewed the patient and implemented management changes based on patients pre-defined goals and the patient's clinical course.

3.3.9.2 *Variables collected*

At recruitment, data was collected on patient age, sex, body mass index (BMI), smoking history, asthma exacerbation history, healthcare use (including general practitioner visit, emergency department visits and the number of hospitalisations in the previous year). Co-morbid medical history including history of rhinitis, sinusitis, gastro-oesophageal reflux disease and other medical diseases were recorded. Prescribed and over the counter medications were recorded at every study visit (study visit 1 to study visit 6) Salmeterol/fluticasone dose was recorded.

3.3.9.2.1 Lung function measurements

Pulmonary function was monitored during the study by measuring the spirometry (FEV_1 (L) and % predicted and FVC). Spirometry was measured using the handheld vitalograph In2initive spirometer in accordance with the ATS/ERS guidelines (252). The spirometer was calibrated daily before use. FeNO measurements were conducted using the Niox VERO. PEFR measurement were conducted using the electronic Vitalograph asma-1 Digital Peak Flow Meter.

3.3.9.2.2 Questionnaires used in the study

Asthma control was assessed with the Asthma Control Test (ACT) questionnaire (Appendix 5). The ACT score ranges from 5 to 25. An ACT>19 (11) indicates well-controlled asthma and a significant improvement is seen with an increase ≥3.0 (253). ACT score of ≤19 indicates poor controlled asthma. Asthma quality of life was assessed using the mini asthma quality of life questionnaire (AQLQ) and the European Quality of life, 5 dimensions, 3 layers (EQ-5D-3L) scores (Appendix 6 and 7). The mini AQLQ questionnaire is a 15-item score that assesses asthma quality of life in four domains (symptoms, activities, emotions and environment) AQLQ score ranges from 1-7 and the score of ≥5 denotes better quality of life and a significant improvement is seen with an increase of ≥0.5 (254). The EQ-5D-3L questionnaire consists of two pages: the EQ-5D descriptive system (first page of the questionnaire) and the EQ-5D visual analogue scale (EQ VAS) (on the second page of the questionnaire), (Appendix 7). The EQ-5D-3L descriptive system comprises five

dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) that describe different aspects of health. Each dimension are described in three levels: no problems; some problems and extreme problems (255, 256). The patient was asked to choose most appropriate statement that describes his/her health status in each of the five dimensions. The EQ VAS provides the patient's self-rated health on a vertical VAS where the endpoints are labelled on a scale of zero to hundred. A score of zero indicate 'the worst health you can imagine' and a score of hundred indicate 'the best health you can imagine'. The information can then be used as a quantitative measure of health outcome The scores of the EQ-5D-3L would subsequently be converted into a single summary number which would reflect how good or bad a health state is according to the preferences of the general population in Ireland and this would facilitate a cost-utility analysis (i.e., facilitate calculation of QALYs that would be used to inform economic evaluations of the INCA intervention).

The Work Productivity and Activity Impairment-Asthma (WPAI-Asthma) questionnaire was used to assess productivity impairment (Appendix 8). The WAPAI- Asthma questionnaire provides a patient's self-reported quantitative assessment of the amount of both absenteeism and presenteeism as well as daily activity impairment attributable to asthma during the past 7 days. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (257)**.** Patients were asked to complete the ACQ, AQLQ and EQ-5D-3L at each study visit 1, 3, 4, 5 and visit 6 while the WAPAI-Asthma questionnaire was also completed at visit 2.

3.3.9.3 *Description of the study population*

The study population was patients 18 years of age or older who had a confirmed diagnosis of asthma which was poorly controlled. Patients had to be prescribed asthma therapy consistent with Stage 3 to 5 of the GINA guidelines which includes treatment with low to high dose ICS/LABA therapy with or without the addition of low dose prednisolone, leukotriene receptor antagonist and tiotropium. Patients who have been treated with ≥1 course of oral corticosteroids (OCS) in the previous year or had a future risk of exacerbations defined by a history of a hospitalisation or emergency department (ED) attendance with an asthma exacerbation in the previous year were enrolled into the study. Patients had to be exacerbation free for at least four weeks prior to recruitment.

3.3.9.4 *Inclusion criteria*

Enrolled patients were 18 years or older, had a confirmed diagnosis of asthma and were managed with therapy consistent with Stage 3 to 5 of the GINA guidelines (111). A confirmed diagnosis of asthma in this study was defined as a clinician diagnosis of asthma supported by any one of the following characteristics: forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) <70% and FEV1<80%, or a 12% improvement in FEV1 post-bronchodilator, or a positive bronchial provocation test or variability in diurnal PEFR of ≥ 15% over a 1-month period. Patients had uncontrolled asthma at recruitment (ACT≤19) and they had been treated for an asthma exacerbation with ≥1 courses of oral corticosteroids in the prior year or have a history of a hospitalisation or emergency department attendance with an asthma exacerbation in the last year. Patients were enrolled if they could understand and comply with the requirements of the protocol, including an ability to attend all required visits, and were willing to give voluntary informed consent before any protocol-specific procedures being performed.

3.3.9.5 *Exclusion criteria*

Patients who were current smokers or ex-smokers with >20 pack year history of smoking were excluded from the study. Further exclusion criteria included: patients who were pregnant or intending to become pregnant; patients with a known hypersensitivity to salmeterol/ fluticasone or fluticasone propionate or salbutamol;

patients on biologic treatment or specific concurrent potent cytochrome P4503A4 medications. Patients who had prior hypersensitivity to salmeterol/ fluticasone, or fluticasone propionate or salbutamol were also not eligible for the study. Patients who had a significant concurrent medical disease that might mean that the participant could not complete the full duration of the study were not enrolled.

3.3.10 ENROLMENT, SCREENING AND RUN-IN PHASE

Patients were enrolled at specialist asthma clinics. Patients with asthma attending emergency departments (ED) or admitted to hospital wards were also recruited. I conducted weekly screening clinics in Beaumont hospital reviewing asthma patients referred by general practitioners. I also attended asthma and general respiratory clinics in Connolly hospital screening and recruiting patients for the study. Patients who were taking other ICS/LABA combination other than salmeterol fluticasone were switched to an equivalent dose of salmeterol/fluticasone during the screening phase of the study. During the screening phase of the study, asthma diagnosis was confirmed by ensuring that pulmonary function tests (PFTs) with a positive bronchodilator response was carried out within a one-year period. PFTs test were organised for patients who never had PFTs and in those with a negative bronchodilator response PEFR monitoring was conducted over a four-week period. If the diagnosis of asthma was not confirmed patients underwent bronchial provocation test of which there was a three-month waiting list and hence the screening phase for an individual could range between a week to three months. Eligibility criteria were also assessed during the screening phase of the study.

After the screening phase was completed patients underwent a run-in period (the first week of the study-**Error! Reference source not found.**). Patients had to be free of an asthma exacerbation for at least four weeks to undergo the run-in period. During the run-in period, eligibility criteria were confirmed, and patients were enrolled into the study after signing informed consent. Patients were given fluticasone propionate in addition to their maintenance salmeterol/ fluticasone dose, and their adherence was monitored for seven days. A 7-day fractionated

exhaled nitric oxide (FeNO) suppression test was used to assess steroid response in the first week of the study (73). Patients were also educated on how to use a PEFR meter, FeNO machine and were provided with inhaler technique training. A video outlining inhaler education is available online (258).

3.3.11 RANDOMISATION

A 7-day FeNO monitoring period was conducted during the run-in phase of the study. During these first seven days, a FeNO suppression test was conducted. All the enrolled patients had FeNO measured at study visit 1 (day 0). In addition to the usual salmeterol/fluticasone propionate dose patients were given additional fluticasone 1000mcg daily via a Diskus with an INCA device. Patients were then asked to perform FeNO measurements daily. Printed instruction manual for the inhaler and the Niox VERO were given to each patient (Appendix 9). At the end of the 7-day monitoring period, patients were randomised in an allocation ratio of 1:1 to receive feedback on inhaler adherence information from the INCA device, PEFR and environmental data or current best practice. Site and day 7 FeNO result stratified the randomisation (FeNO ≥45ppb or FeNO <45ppb). The allocation was a computer-generated permuted block design, with blocks varying in size of 2, 4 and 6. The randomisation schedule was developed by a statistician and an independent clinical informatics manager using a computer-generated randomisation programme as detailed on the website www.randomisation.com. A password-controlled Excel file containing the randomisation schedule for each site was available for different sites. The researcher entered the patient/subject ID number and FeNO in the Excel file and the group of the trial to which the patient is assigned was revealed.

3.3.12 BLINDING

Both the study participants and the researchers delivering the educational interventions were not blinded to treatment allocation because of the nature of the education intervention. To avoid the risk of contamination between the active and

the control group, the researchers delivering the education (best practice) to the control group patients did not have access to the INCA device data. The researcher had access to INCA device data for the active group. The data outcome assessors were blinded to study subject treatment allocation.

3.3.13 DEVELOPMENT OF THE PHYSICIAN SCRIPT

During the second phase of the study, medication adjustment was guided by the integration of clinical progress and objectively assessed adherence for the active group and Global Initiative Asthma (GINA) guidelines with neither recorded adherence nor digitally integrated clinical progress for the control group. A physician script was designed for both the active and control groups based on the GINA control-based asthma management cycle which involves pharmacological and non-pharmacological treatment adjustment in a continuous cycle (Appendix 10)that involves assessment, treatment and review (4). To achieve good control of symptoms patients were assessed using ACT score at every visit. Exacerbations in the preceding months were assessed; lung function was measured to monitor the future risk of exacerbations and fixed airflow obstruction. Medication side-effects were also reviewed at each visit. Patients' goals were incorporated into the visit to assess the maintenance of regular activity as perceived by the patient. If asthma control was maintained for three months treatment could be adjusted. Asthma control was defined by a PEFR persistently ≥80% personal best or an exacerbation free period for three months. Before treatment adjustment, the individual had to be assessed and treated for an acute asthma exacerbation and co-morbidities had to be treated. Once co-morbidities have been optimised, treatment could be adjusted whereby the dose of salmeterol/fluticasone propionate could be increased from 250 micrograms (mcg) to 500 mcg or patient could be referred for Step- 5 GINA recommended therapy (Appendix 11)(4). The dose of the salmeterol/fluticasone was either 50/500mcg or 50/250; therefore, the dose of salmeterol/fluticasone propionate could only be reduced to 250mcg. If patients were on maintenance prednisolone the dose of prednisolone was decreased first. There are no established guidelines for OCS dose reduction in patients requiring

maintenance OCS, and hence the prednisolone dose reduction was based on Bel et al.'s paper (95) as shown in **Error! Reference source not found.**.

Table S2. Glucocorticoid Reduction Phase Scheme

Sequential Time Course	Glucocorticoid Reduction Phase								
	Prednisone Dose (mg/day)								
Optimized Prednisone Dose	35	30	25	20	15	12.5	10.0	7.5	5.0
1st dose reduction	25.0	20.0	15.0	10.0	10.0	10.0	5.0	5.0	2.5
+ 4 Weeks	15.0	10.0	10.0	5.0	5.0	5.0	2.5	2.5	1.25*
+ 4 Weeks	10.0	5.0	5.0	2.5	2.5	2.5	1.25*	1.25*	0
+ 4 Weeks	5.0	2.5	2.5	1.25*	1.25*	1.25*	0	0	0
+ 4 Weeks	2.5	2.5	2.5	0	0	0	0	0	0

* Taken as 2.5mg administered every other day

Figure 3-2 Criteria for reducing oral corticosteroids

The physician script was developed by the author and a group of asthma specialist experts. This group included the principal investigator and sub-principal investigators from the study sites participating in the study. Using the GINA control-based asthma management cycle we felt that a physician script that incorporates assessing and treating asthma co-morbid disease, adherence, psychosocial factors and optimisation of asthma medical treatment in a stepwise approach is essential. International guidelines recommend the identification and treatment of comorbidities as part of the treatment of patients with severe asthma (4, 259).

These comorbidities include obesity, smoking, aspirin intolerance, rhinitis, gastroesophageal reflux disease, psychological problems such as anxiety and depression and other respiratory diagnoses such as allergic bronchopulmonary aspergillosis and chronic obstructive pulmonary disease. The role of comorbidities in modulating the severity of asthma has been studied. Upper airway disease such as allergic or non-allergic rhinitis and sinusitis are associated with asthma. It has been stipulated that rhinitis can influence asthma by the release of mediators into the airways or peripheral circulation. Braunstahl et al. (260) have shown that segmental bronchial allergen provocation caused peripheral blood eosinophilia and induction of allergic inflammation in the nose in patients' allergic rhinitis without a history of asthma. Nasal allergen provocation in patients with allergic rhinitis caused generalised airway inflammation through upregulation of adhesion molecules. This means that nasal and bronchial inflammation are interrelated, probably through a systemic effect (260). Adults with asthma and concomitant rhinitis have frequent healthcare use (261, 262). so, treating rhinitis may lead to improved asthma control and quality of life (263, 264).

Patients with severe asthma may have chronic rhinosinusitis, and their asthma may prove 'difficult to control'. Extensive sinus disease was found in 24% of patients with severe asthma (265). These patients were found to have increased exhaled nitric oxide, blood eosinophils and induced sputum eosinophils (265). Nasal polyposis and aspirin intolerance has been reported in Ď5% of patients with a severe phenotype of asthma (266) Nasal polyps have been associated with an increased production of cytokines such as interleukin (IL)-5, growth and

chemotactic factors, such as granulocyte-macrophage colony-stimulating factor, eosinophil cationic protein and eotaxin which promote chemotaxis, migration and activation of eosinophils (267). Furthermore, in patients with concomitant asthma and nasal polyposis, increased numbers of bronchoalveolar lavage eosinophils and eosinophil peroxidase-staining cells have been reported in those with airway hyperresponsiveness (268).

A significant association of asthma and GORD has been reported (269). There are several mechanisms in which reflux can induce airway hyperresponsiveness. These include vagus mediated reflexes, chronic micro-aspiration of gastric fluid into the airways, and airway neurogenic inflammatory responses. Despite the association of asthma and GORD, improvement in asthma following GERD treatment is variable. Littner and colleagues' (269) found that in adult patients with moderate to severe persistent asthma and symptoms of acid reflux, treatment with lansoprazole for 24 weeks improved asthma-related quality of life and reduced exacerbations but did not improve asthma control. Asthma control in this study was assessed by assessment of symptoms, pulmonary function or rescue medication use. This means that it may be difficult to assess the effects of GORD on asthma because the improvement of asthma following treatment of GORD varies from patient to patient (269, 270). Therefore, at individual level medication trial may be useful to assess the effects of GORD on asthma control.

Increased prevalence of asthma has been found in obese patients, particularly in females' (271, 272). Obesity is associated with poor asthma control (273) and may intensify asthma severity (274). Furthermore, obesity is associated with the development of OSA and GORD, which are both related to a severe phenotype of asthma. This phenotype is characterised by breathing at low lung volumes, a systemic inflammatory process that influences airway inflammation (275, 276)and a tendency to ICS resistance (277, 278). In a study by Mosen (279) patients with high body mass index (BMI) were more likely to report poor asthma related quality of life, poor asthma control and a history of asthma-related hospitalisations as compared with controls with normal BMI. Lessard et al. (276) observed 88 obese and nonobese individuals and showed that obese asthmatic patients had worse

asthma control, and low lung volumes (expiratory reserve volume, residual volume and functional residual capacity) than nonobese asthmatics despite similar symptoms perception. A high prevalence of obstructive sleep apnoea (OSA) has been reported in patients with severe unstable asthma requiring frequent oral corticosteroid therapy(280). OSA has been associated with increased bronchial neutrophilia and a high IL-8 concentration on sputum analysis in patients with untreated OSA compared with controls (281). Lafond et al. (282) have reported improvement in asthma quality of life in patients with concomitant asthma and OSA after 6-weeks of treatment with nocturnal continuous positive airway pressure treatment. Therefore, interventions to induce weight loss, such as either surgical or diet-induced weight loss may improve asthma outcomes.

Psychological factors such as anxiety, depression and panic disorders are more prevalent in asthma compared with the general population (283). Psychological factors may trigger asthma symptoms as well as affecting patients' perception of symptoms and therefore, lead to frequent health care use (284). Chetta et al. (285) have shown that asthma symptom scores correlated better with the degree of anxiety and depression than with lung function, implying that the interpretation of symptoms may be more pertinent than the degree of physiological impairment. Furthermore, depression, which is commonly prevalent in asthmatics has been associated with poor adherence to medication (286), loss to follow-up (218) and asthma death (287), and thus should be identified and treated (288). Depression and anxiety disorders can occur independent of asthma but may consequently occur because of uncontrolled asthma (288, 289). Dyspnoea has been shown to correlate with anxiety trait and a prospective community-based cohort study of asthmatic subjects aged 19 and 40years, suggested that asthma was associated with anxiety and panic disorder (290). This study also showed that after adjusting for confounding variables, active asthma was a predictor of subsequent panic disorder (289).

A pilot study conducted in ten asthmatic patients with anxiety and panic disorder showed significant decreases of >50% in panic symptoms, clinically significant decreases in asthma symptoms, improvement in asthma quality of life, and

maintenance of clinical stability in asthma (291). The patients underwent 14 weeks and 8-week session protocol which included: relaxation and breathing training; asthma education; cognition restructuring; treatment of agoraphobic symptoms; education on asthma and panic disorder; education on effective communication with doctors and smoking cessation. This study suggests that potentially treatment of psychological disorders may improve asthma outcomes. However, a systematic review by Fleming et al (292) was unable to draw firm conclusions about the efficacy of psychotherapeutic interventions for adults with asthma. It is worth noting that the review was limited by poor quality of the studies and small sample sizes.

Hyperventilation syndrome and paroxysmal vocal dysfunction (PVCD) often associated with anxiety may mimic asthma. Laryngoscopy proven PVCD has been reported to coexist with asthma in 56% patients fulfilling the criteria of paradoxical vocal cord motion disorder (293), may coexist with both asthma and GORD and there is a female predominance (293). PVCD is often misdiagnosed as treatment-resistant asthma and the diagnosis can be delayed for up to five (293) to nine years (294). Because these patients are misdiagnosed as having severe asthma and they often require treatment with bursts of oral corticosteroids; have multiple emergency room visits, hospitalisations, and in some cases (28%) require tracheal intubation (293, 294). Undiagnosed respiratory conditions such as chronic obstructive pulmonary disease (COPD) and Allergic bronchopulmonary aspergillosis (ABPA) may coexist in patients with asthma and may contribute to poor asthma control. Asthmatics who are smokers may develop COPD and hence can influence the underlying phenotype and treatment response (295). ABPA, which is occasionally observed in patients with severe asthma may contribute to asthma that is ‘refractory’ to treatment (296). Therefore, it is essential to identify and treat comorbid respiratory disease when managing patients with asthma.

The conditions described above may modulate asthma severity in various ways. For example, obesity, smoking, aspirin intolerance and allergic bronchopulmonary aspergillosis may suggest a different phenotype of asthma while upper airway disease such as rhinitis may suggest a similar pathophysiological process as asthma.

Therefore, a physician assessment tool (physician script) that incorporates the identification and treatment of comorbid asthma disease was developed for the study.

Fortnightly meetings were held over a three months period during which the physician's script was tested over hypothetical scenarios which were created from a pool of clinical cases that have been proven to be difficult to manage in the clinical setting. The physician script was tested and re-evaluated until a consensus was reached to formulate the final script to be used in the study. A flow diagram of the physician script is shown in Figure 3-3. A detailed physician script used when conducting visit 4 to 6 is described below.

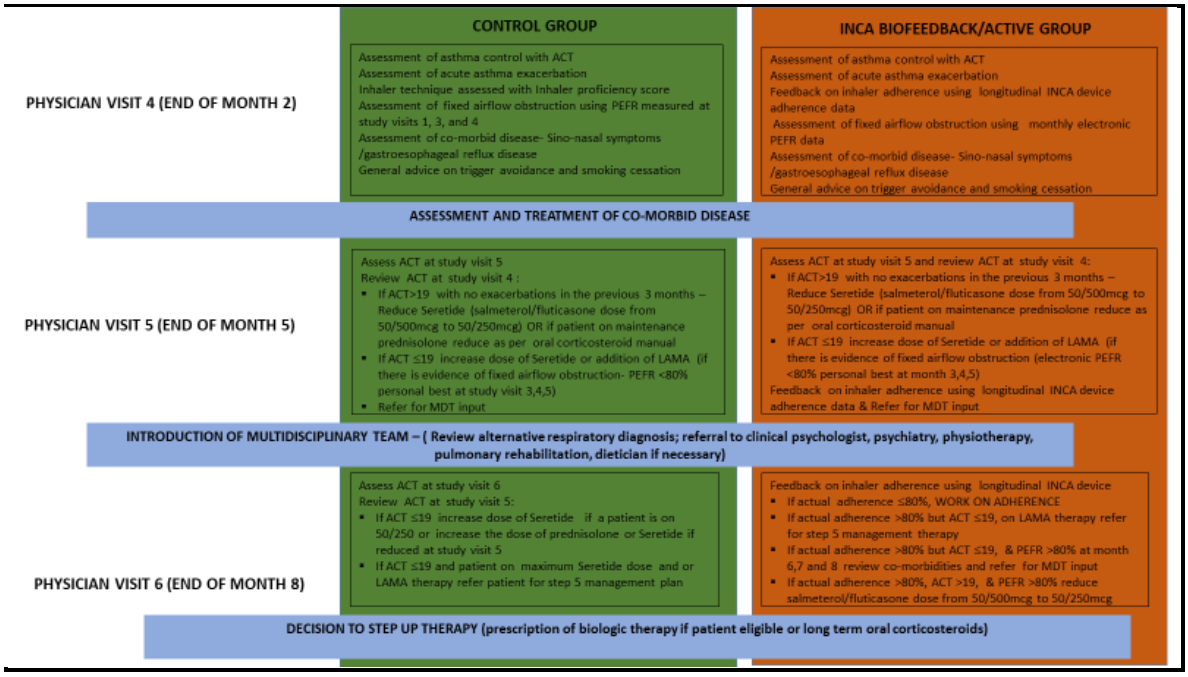


Figure 3-3 Flow diagram of the physician script

3.3.13.1 *Visit 4 control group*

Following a nursing visit, the information collected from the patient included ACT score, PEFR data at visit 1, 3 and 4 and exacerbation history between visits 1 and 4. The current prescribed dose of salmeterol/fluticasone propionate was documented. The patient's personal best PEFR was the recorded as the highest PEFR during the run-in (visit 1 to visit 2) period of the study.

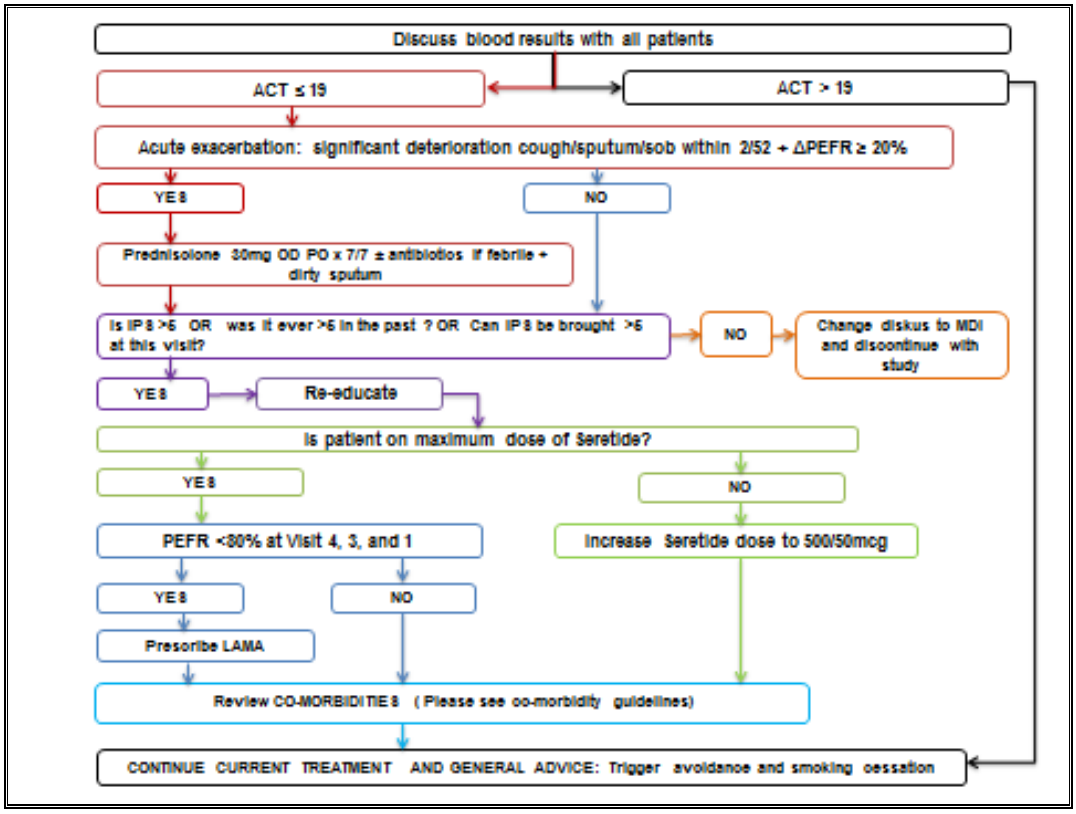


Figure 3-4 Visit 4 physician script for the control group

For a patient allocated to the control group the first step was to assess asthma control using the ACT. There were two algorithms: one for patients with ACT ≤19 and another for patients with ACT of >19 (Figure 3-4).

If the ACT was more than 19 at study visit 4 the patient was advised to continue current Seretide dose and general advice including trigger avoidance and smoking cessation was offered.

If the ACT was ≤19 (Figure 3-4) the following steps were followed:

1. Assessment of acute exacerbation of asthma was done. An acute exacerbation was defined by a significant deterioration in cough, sputum, dyspnea within a 2-week period associated with a change in PEFR of ≥20%. A change in PEFR was calculated as follows:

2. After assessment of an exacerbation the next step was to assess inhaler adherence using the inhaler proficiency score (IPS). The IPS is a ten-point check list for assessing inhaler technique for the Diskus inhaler (Figure 3-5). The IPS assess the 3 domains of correct Diskus inhaler use: priming, inhalation and post-inhalation. IPS score of ≥ 6 signify correct Diskus inhaler use while IPS score of <6 indicate poor Diskus inhaler use. If the IPS was <6 at visit 4 and previous study visits 1, 2 and 3 despite efforts to educate the patient on Diskus inhaler use, the patient could no longer participate in the study. Patient would be prescribed MDI device and excluded from the study. If the patient's IPS was more than 6, the following steps were then followed:

a) Salmeterol/fluticasone propionate dose was reviewed to ensure if patient was uncontrolled (ACT≤19) despite maximum dose of 500/50mcg.

b) If patient was prescribed Salmeterol/fluticasone propionate dose of 250/50mcg the dose was increased to 500/50mcg. For a patient who was already (prior to study visit 4) prescribed salmeterol/fluticasone propionate dose of 500/50mcg, PEFR at study visits 1, 3 and 4 were reviewed to assess for fixed airflow obstruction defined as PEFR of <80% personal best PEFR. If the PEFR was <80% personal best patient was prescribed a long acting muscarinic antagonist (LAMA) inhaler.

c) Co-morbidities including gastro-esophageal reflux and reflux were assessed and treated as outlined in the co-morbidity step-by step guide (Figure 3-6).

General advice including trigger avoidance and smoking cessation was offered. The study visit was then completed, and patient was given appointments for the next study visits and dispensing visits.

Patient ID: _____

Date: _____

Visit No: _____

		YES	NO
	Does the patient hold the outer casing of the inhaler in one hand, whilst pushing the thumb grip away, until a click is heard?		
	Does the patient hold the inhaler with mouthpiece towards himself?		
	Does the patient slide lever away until it clicks?		
	Does the patient hold the inhaler in a horizontal position?		
	Does the patient breath out slowly and then put inhaler in front of mouth?		
	Does the patient place mouthpiece between lips and breathe in as deeply as possible?		
	Does the patient remove inhaler from mouth and hold breath for about 10 seconds?		
	After 10 seconds does the patient breathe out slowly?		
	Does the patient close the inhaler by sliding thumb grip back towards him as far as it will go until it clicks?		
	Does the patient gargle throat after use?		

Figure 3-5 Inhaler Proficiency Schedule (IPS)

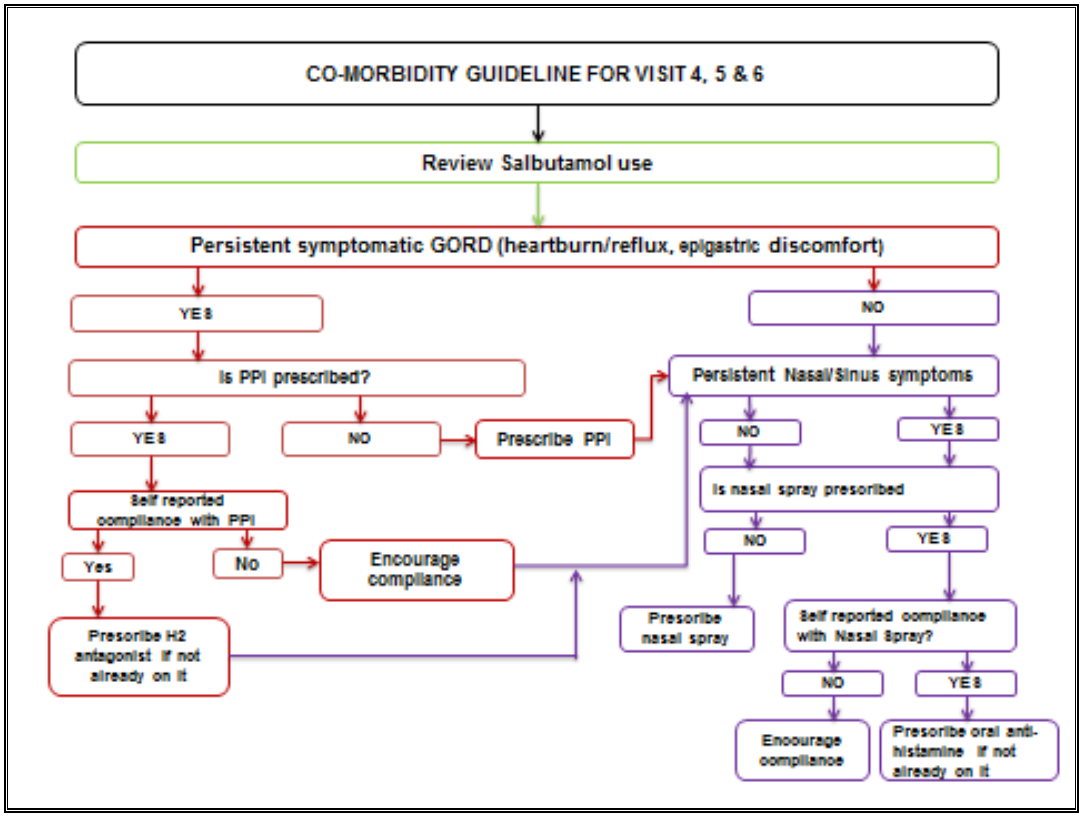


Figure 3-6 Co-morbidity guideline

3.3.13.2 *Visit 5 control group*

Following a nursing visit at study visit 5, the information collected from the patient who was allocated to the control group included ACT score, PEFR data at visit 4 and 5 and exacerbation history between visits 4 and 5. The current prescribed dose of salmeterol/fluticasone propionate was documented. If there were medication changes between visit 4 and visit 5, these would be recorded.

At visit 5 the physician assessed asthma control using the ACT. There were two algorithms: one for patients with ACT ≤19 (Figure 3-7); and the other for patients with the ACT of >19 (Figure 3-8).

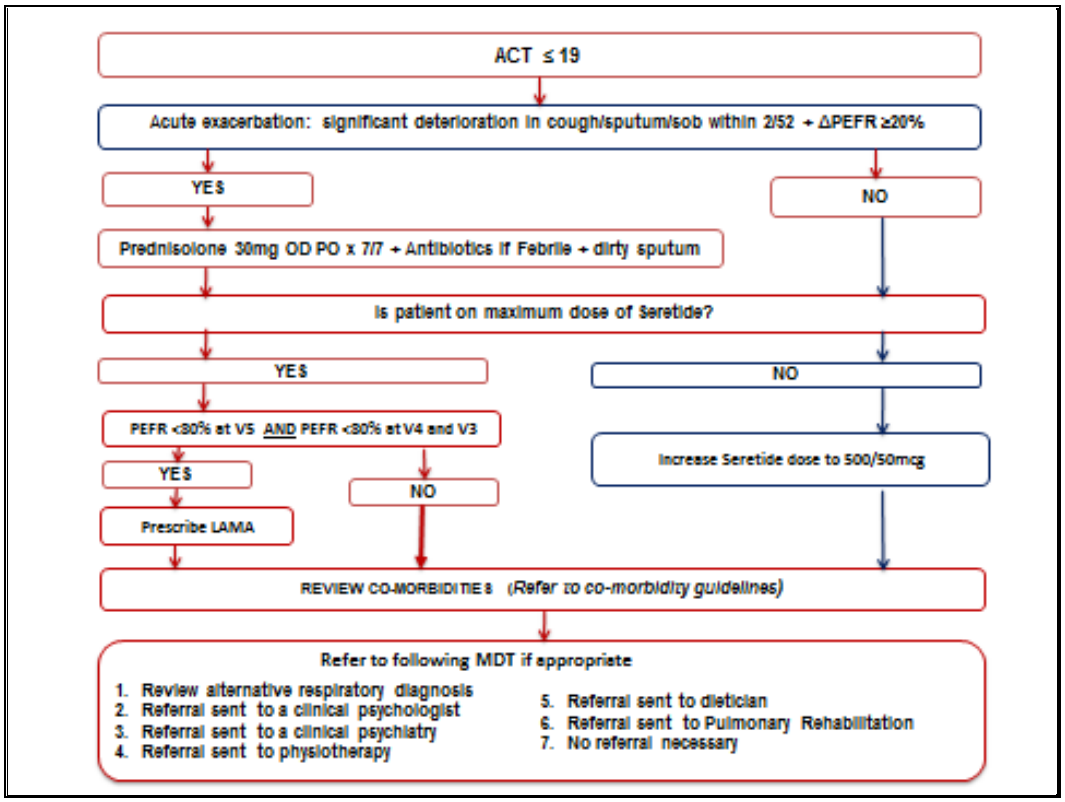


Figure 3-7 Visit 5 physician script for the control group (ACT ≤19)

If the ACT was ≤19 (Figure 3-7) assessment of acute exacerbation of asthma was done. An acute asthma exacerbation was defined by a significant deterioration in cough, sputum, dyspnoea within a 2-week period associated with a change in PEFR of ≥20%. A change in PEFR was calculated as follows:

$$\text{Change in PEFR} = \frac{\text{Highest PEFR recorded during exacerbation} - \text{Lowest PEFR recorded during exacerbation}}{\text{Highest PEFR recorded during exacerbation}}$$

If the patient did not have an acute exacerbation of asthma the following steps were followed:

1. Salmeterol/fluticasone propionate dose was reviewed to ensure if patient was uncontrolled (ACT≤19) despite maximum dose of 500/50mcg.
2. If patient was prescribed Salmeterol/fluticasone propionate dose of 250/50mcg the dose was increased to 500/50mcg. If a patient was already

(prior to study visit 5) prescribed salmeterol/fluticasone propionate dose of 500/50mcg, PEFR at study visits 3, 4 and 5 were reviewed to assess for fixed airflow obstruction defined as PEFR of less than 80% of the personal best PEFR. If the PEFR was <80% personal best patient was prescribed a long acting muscarinic antagonist (LAMA) inhaler.

3. Co-morbidities including gastro-esophageal reflux and reflux were assessed and treated as outlined in the co-morbidity step-by step guide (Figure 3-6).
4. Multidisciplinary team referral involving specialties such as psychiatry, psychology physiotherapy and dietetics were conducted as appropriate. For example, patient who had underlying depression which may have contributed to uncontrolled asthma, were referred to psychiatrist and for a patient with co-existing dysfunctional breathing or bronchiectasis were referred see a respiratory physiotherapist.

If an acute exacerbation was confirmed at study visit 5, patient was commenced on a 7-day course of prednisolone and antibiotics prescription was added if the patient was febrile and reported production of purulent sputum. The subsequent steps that were followed are outlined from 1 to 5 above.

If the ACT was more than 19 (Figure 3-8) the following steps were followed:

1. ACT for visit 4 was reviewed and if a patient ACT was ≤19 patients continued their treatment without adjustment of their therapy. This treatment could either be fluticasone/salmeterol 50/500mcg or 50/250mcg dose. The study visit would be completed and visit 6 was scheduled for three months later. Dispensing visits were scheduled monthly.
2. If the patients' ACT was more than 19, at study visit 4, exacerbation history and PEFR data were reviewed.
3. If the patient had no exacerbations in the prior three months OR the PEFR was more than 80% of patients' personal best at visit 5 and 4 the fluticasone/salmeterol 50/500mcg dose could be reduced to 50/250mcg.

Prednisolone was tapered first in patients who were on maintenance prednisolone (**Error! Reference source not found.**). The study visit was completed and visit 6 was scheduled.

4. If a patient had an exacerbation in the previous three months OR the PEFR was more than 80% of patients' personal best at either visit 4 or 5 the patient continued their treatment without adjustment of their therapy.
5. All the patients were offered advice on trigger avoidance and regular exercise.

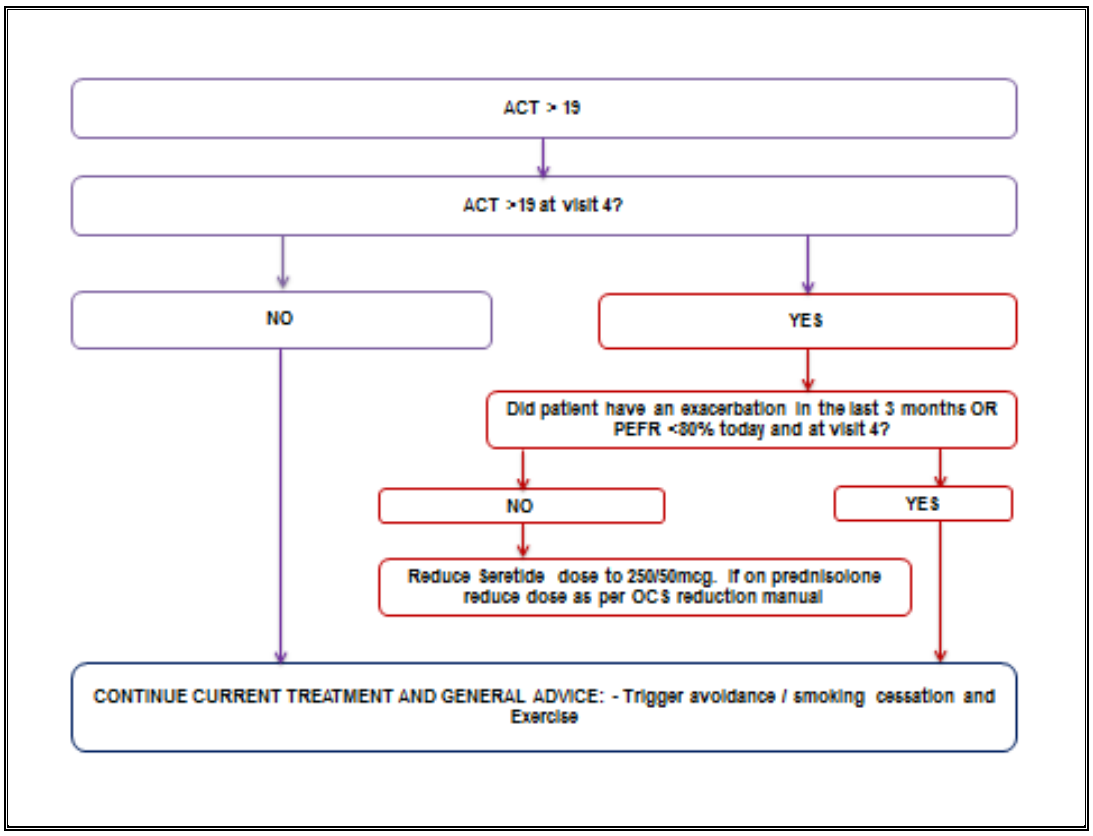


Figure 3-8 Visit 5 physician script for the control group (ACT >19)

3.3.13.3 *Visit 6 control group*

At visit 6 the physician assessed asthma control using the ACT. There were two algorithms: one for patients with ACT ≤19 (Figure 3-9) and the other for patients with the ACT of >19 (Figure 3-11).

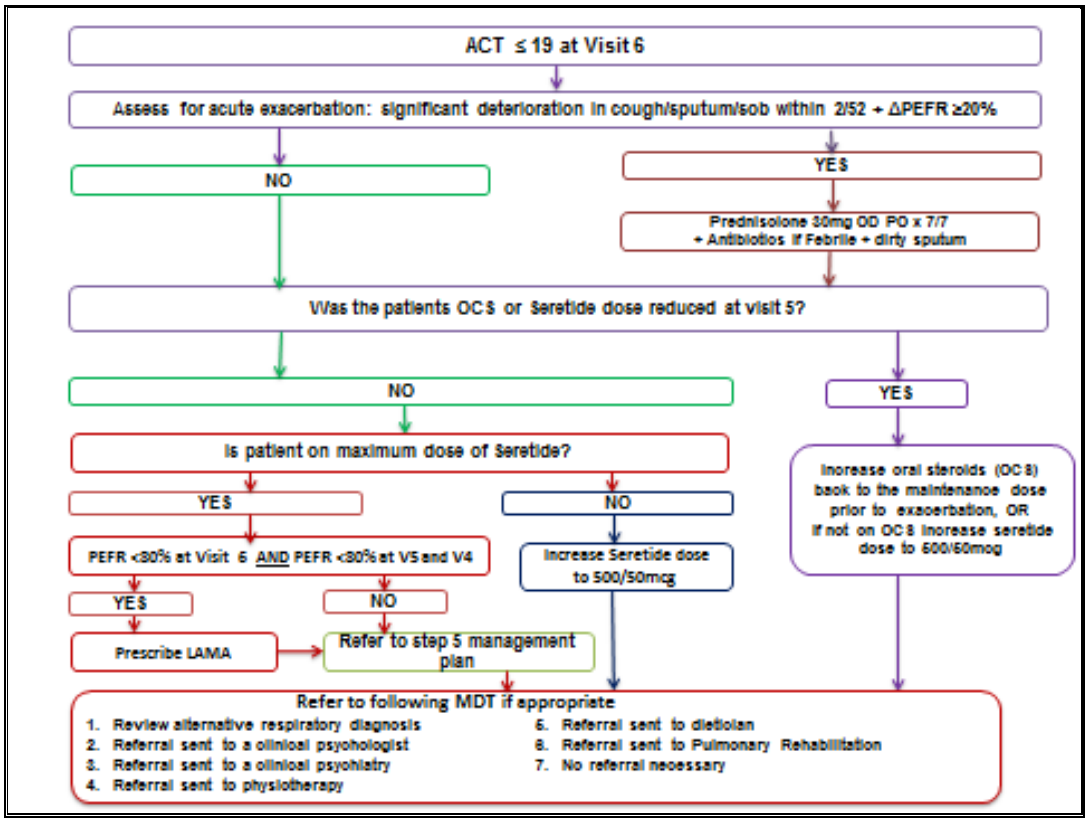


Figure 3-9 Visit 6 physician script for the control group (ACT ≤19)

If the ACT was ≤19 (Figure 3-9) assessment of acute exacerbation of asthma was done. If an acute exacerbation was confirmed at study visit 6, patient was commenced on a 7-day course of prednisolone and antibiotics prescription was added if the patient was febrile and reported production of purulent sputum. If the patient did not have an acute exacerbation of asthma or the patient was prescribed appropriate medications for an exacerbation of asthma, the following steps were followed:

1. Assessment of salmeterol/fluticasone propionate dose was reviewed to ascertain if reduction of the dose from 500/50mcg to 250/50mcg at study visit 5 could have resulted in poor control of asthma (ACT≤19).
    - Á If the patient was on maintenance OCS, review of previous dose adjustment was assessed, and the dose of prednisolone was increased. If the dose of salmeterol/fluticasone propionate dose was previously reduced at study visit 5, the dose was then increased to 500/50mcg.
    - Á If at visit 6, the patient was prescribed Salmeterol/fluticasone propionate dose of 250/50mcg the dose was increased to 500/50mcg.
    - Á If a patient was already (prior to study visit 6) prescribed salmeterol/fluticasone propionate dose of 500/50mcg, PEFR at study visits 4, 5 and 6 were reviewed to assess for fixed airflow obstruction defined as PEFR of less than 80% of the personal best PEFR. If the PEFR was <80% personal best patient was prescribed a long acting muscarinic antagonist (LAMA) inhaler.
    - Á If a patient was already on salmeterol/fluticasone propionate dose of 500/50mcg, with no evidence of fixed airflow obstruction (defined as PEFR of less than 80% of the personal best PEFR) or patient was on LAMA therapy patient was referred for step-up therapy (Figure 3-10)
2. Multidisciplinary team referral involving specialties such as psychiatry, psychology physiotherapy and dietetics were conducted as appropriate. For example, patient who had underlying depression which may have contributed to uncontrolled asthma, were referred to psychiatrist and for a patient with co-existing dysfunctional breathing or bronchiectasis were referred see a respiratory physiotherapist.

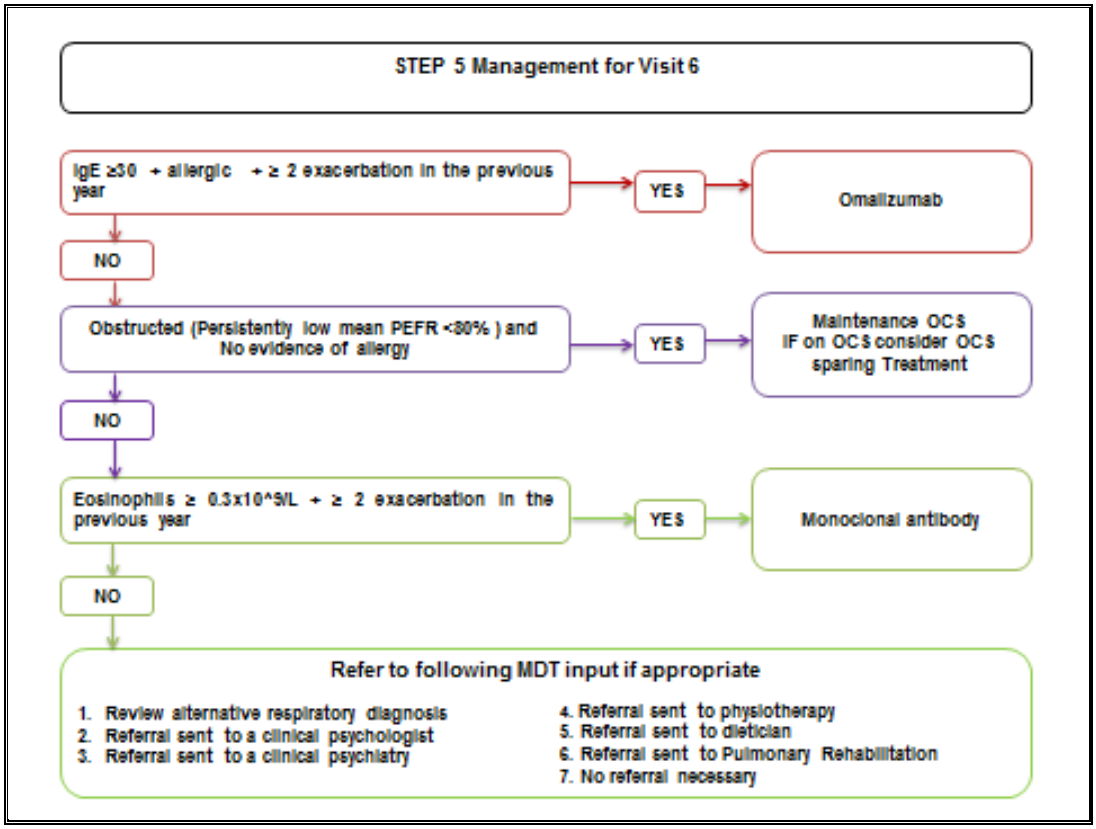


Figure 3-10 Visit 6 Step-up Management therapy

If the ACT was more than 19 (Figure 3-11) at study visit 6, the following steps were followed:

1. ACT for visit 5 was reviewed and if a patient ACT was ≤19 patients continued their treatment without adjustment of their therapy. This treatment could either be salmeterol/fluticasone 50/500mcg dose or 50/250mcg dose. The study visit would end, and study completion form was completed by the investigator.
2. If the patients' ACT was more than 19, at study visit 5, exacerbation history and PEFR data were reviewed.
3. If the patient had no exacerbations in the prior three months OR the PEFR was more than 80% of patients' personal best at visit 5 and 4 the salmeterol/fluticasone 50/500mcg dose could be reduced to 50/250mcg. Prednisolone was tapered first in patients who were on maintenance prednisolone (**Error! Reference source not found.**). General advice on

trigger avoidance and regular exercise was offered to the patient. The study visit would end, and study completion form was completed by the investigator. If a patient had an exacerbation in the previous three months; OR the PEFR was more than 80% of patients' personal best at either visit 4 or 5; AND the salmeterol/fluticasone dose was reduced at study visit 5, then salmeterol/fluticasone dose was increased to 50/250mcg. However, if there was no dose reduction in either the prednisolone or salmeterol/fluticasone dose the patient continued the current ICS or prednisolone dose. All the patients were offered advice on trigger avoidance and regular exercise. The study visit would end, and study completion form was completed by the investigator.

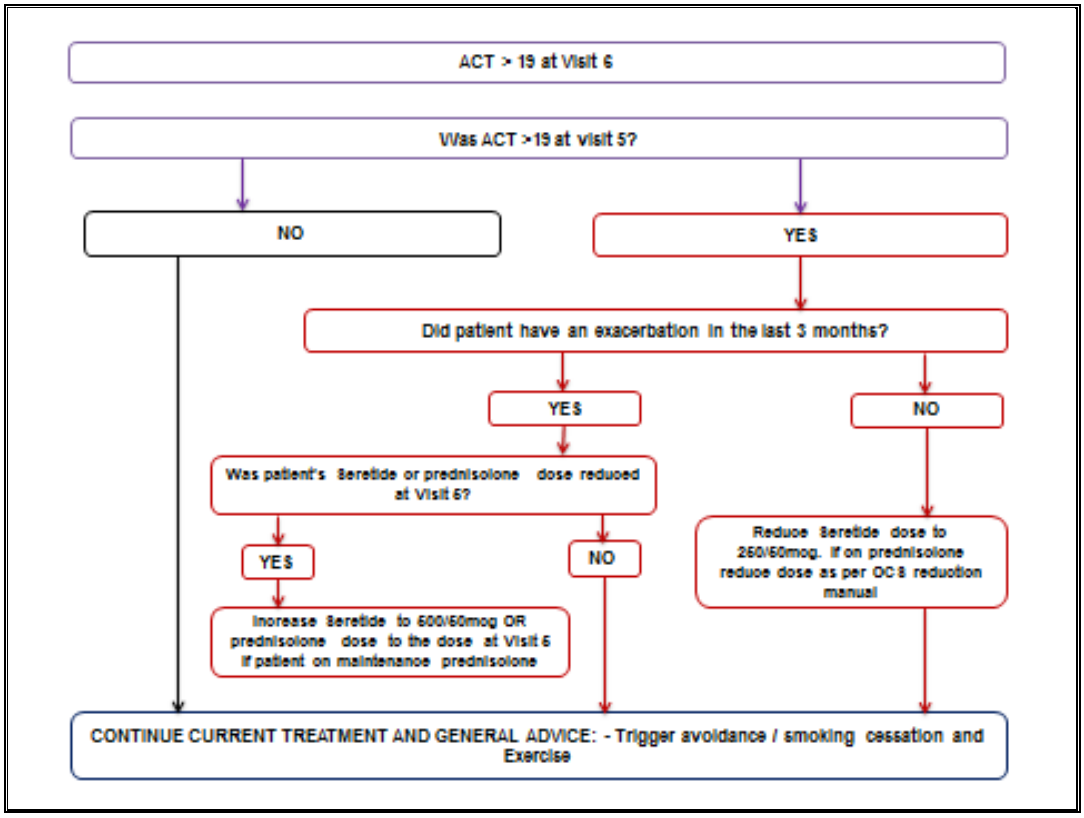


Figure 3-11 Visit 6 physician script for the control group (ACT >19)

3.3.13.4 *Visit 4 active group*

Following a nursing visit, the information collected from the patient included ACT score, electronic PEFR data at visit 1, month 1 (study visit 3), and month 2(study visit 4) and exacerbation history between visits 1 and 4. The current prescribed dose of salmeterol/fluticasone propionate was documented. The patient's personal best PEFR was the recorded as the highest PEFR during the run-in (visit 1 to visit 2) period of the study. Adherence data from the INCA device for month 1 and month 2 was used to provide feedback on inhaler use.

For a patient allocated to the INCA biofeedback group (active group), the adherence was calculated before the physician could review the patient. Adherence was calculated by an automated algorithm saved in the webserver and the output was the attempted adherence rate and the actual adherence rate. This method of calculating adherence has been described by the INCA study group (237). Briefly, the attempted adherence rate was defined as the number of doses that the patient attempt to take as a percentage of the expected doses (the total number of the doses as per the dose counter on the salmeterol/fluticasone propionate Diskus inhaler). The attempted adherence rate includes all the doses taken as per the evidence of drug priming in the acoustic analysis regardless of whether the inhaler was taken with or without the correct technique. The actual adherence was the doses taken with the correct inhaler technique and time intervals relative to the expected drug accumulation if adherence and technique were correct. The actual adherence rate was used for the physician script.

At study 4 visit, there were two algorithms that could be followed; one for patients with adherence of <80% (Figure 3-12) or adherence of ≥80% (Figure 3-13).

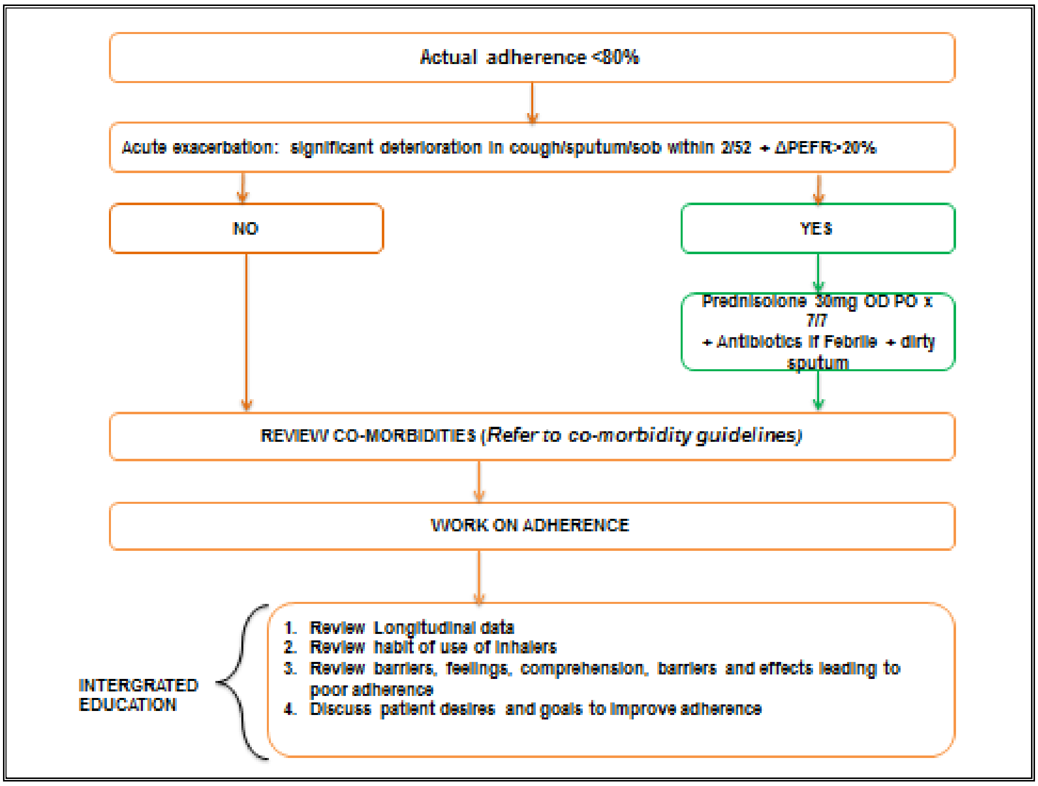


Figure 3-12 Visit 4 physician script for active group (actual adherence <80%)

If the patient's actual adherence was <80%, assessment of acute exacerbation of asthma was done. An acute exacerbation was defined by a significant deterioration in cough, sputum, dyspnoea within a 2-week period associated with a change in PEFR of ≥20%. A change in PEFR was calculated as follows:

õΏὤ ἐ "ΏΏἕ ΌΌ ...

If an acute exacerbation was confirmed at study visit 5, patient was commenced on a 7-day course of prednisolone and antibiotics prescription was added if the patient was febrile and reported production of purulent sputum. After assessment of asthma exacerbation, the following steps were followed:

- Co-morbidities including gastro-esophageal reflux and reflux were assessed and treated as outlined in the co-morbidity step-by step guide (Figure 3-6).

- Integrated inhaler education was offered to the patient. The patient was advised to 'WORK ON ADHERENCE'. This was done by reviewing longitudinal data (INCA device adherence data and electronic PEFR data), identifying the barriers or causes of poor adherence and addressing them as well as achieving a shared decision with a patient to improve adherence. This included discussing the patient's desires and setting meaningful goals to improve adherence. Some of the important goals for the patient's included 'being able to go dancing', 'being able to play with grand-children without experiencing breathlessness', and reduction in the dose of salmeterol/fluticasone or a decrease in SABA use.

If the patient's actual adherence was ≥ 80% (**Error! Reference source not found.**) ACT and electronic PEFR data was reviewed. There were three possible scenarios that could be followed:

Scenario 1: ACT ≤19, and mean PEFR month 2 (visit 4) ≥80% of patient's personal best.

Scenario 2: ACT>19, and mean PEFR month 2 (visit 4) ≥80% of patient's personal best.

Scenario 3: ACT ≤19 or ACT>19 but PEFR ≤80% of patient's personal best.

Patients who were categorised into scenario 1 or 2, received inhaler education. Longitudinal data from the INCA device was used to deliver inhaler education. Blood results such as eosinophil count, RAST IgE were discussed with the patient. Co-morbidities were assessed, and treatment adjusted appropriately (Figure 3-6). In addition to inhaler education, discussing blood results and review of co-morbidities, the salmeterol/fluticasone dose and assessment for fixed airflow obstruction was done for patients categorised into scenario 3. If the patient was on salmeterol/fluticasone dose of 50/250mcg, the dose was increased to 500mcg. If the patient's mean PEFR of <80% at month 1 and month 2, patient was commenced on LAMA therapy. Patients who were on LAMA therapy before visit 4, adherence to

LAMA therapy was addressed. The study visit will be completed and visit 5 will be scheduled for three months from the study visit 4 date.

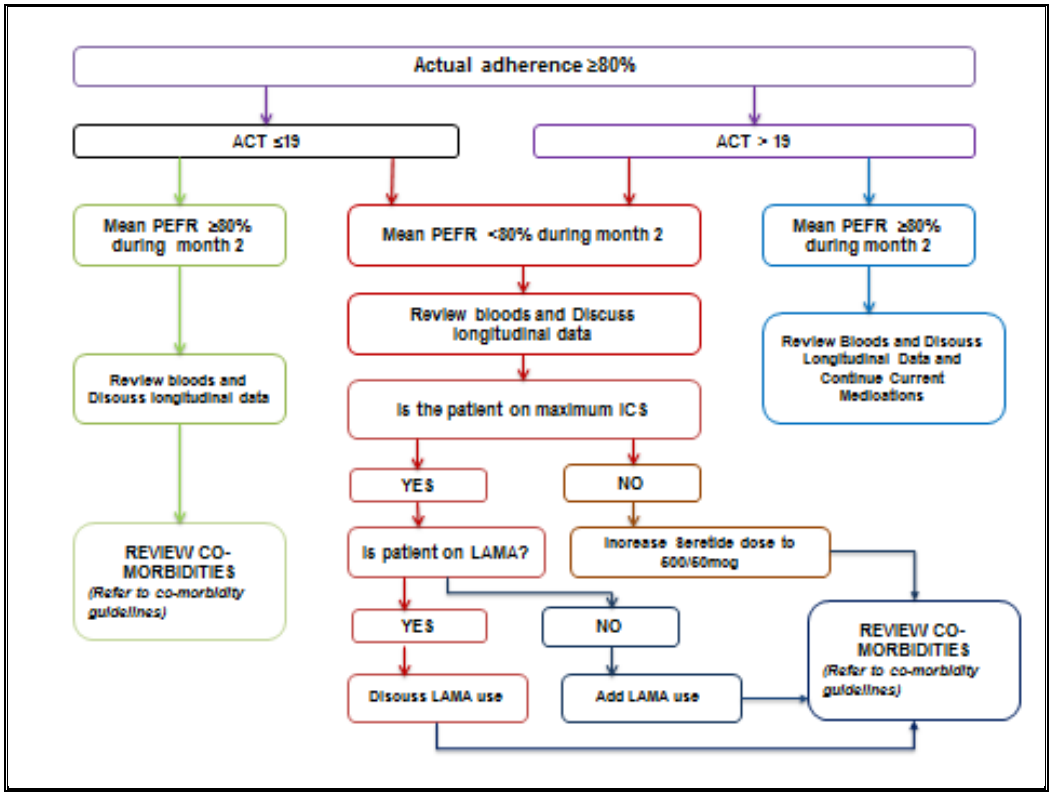


Figure 3-13 Visit 4 physician script for active group (actual adherence ≥80%)

3.3.13.5 *Visit 5 active group*

At study visit 5 if the patient's adherence was <80% an assessment of an acute exacerbation of asthma was done and exacerbation was treated with a seven-day course of prednisolone 30mg daily. A seven-day course of antibiotics was prescribed if patient reported pyrexia and production of purulent sputum. Asthma control was assessed using the ACT score and there were three possible scenarios;

Scenario 1: actual adherence <80% and ACT≤19

Scenario 2**:** actual adherence <80%, ACT>19 and mean PEFR <80% at month 5

Scenario 3: actual adherence <80%, ACT>19 and mean PEFR ≥80% at month 5

Co-morbidities were assessed and addressed for the patients categorised into scenario 1. Patients' were then advised to 'WORK ON ADHERENCE'. An example of using longitudinal data from the INCA device to 'WORK ON ADHERENCE' is illustrated in Figure 3-15 and Figure 3-16.

Patients' who were categorised into scenario 2 and 3 were advised to work on adherence by providing inhaler feedback education from the INCA device. However, the dose of salmeterol/fluticasone was reduced from 50/500 to 50/250 (or reduction of dose of maintenance prednisolone for patients on prednisolone) for the patients who were categorised into scenario 3 because asthma was well controlled (ACT>19) and the lung function was good (mean PEFR ≥80%). The study visit will be completed and visit 6 will be scheduled in the subsequent three months.

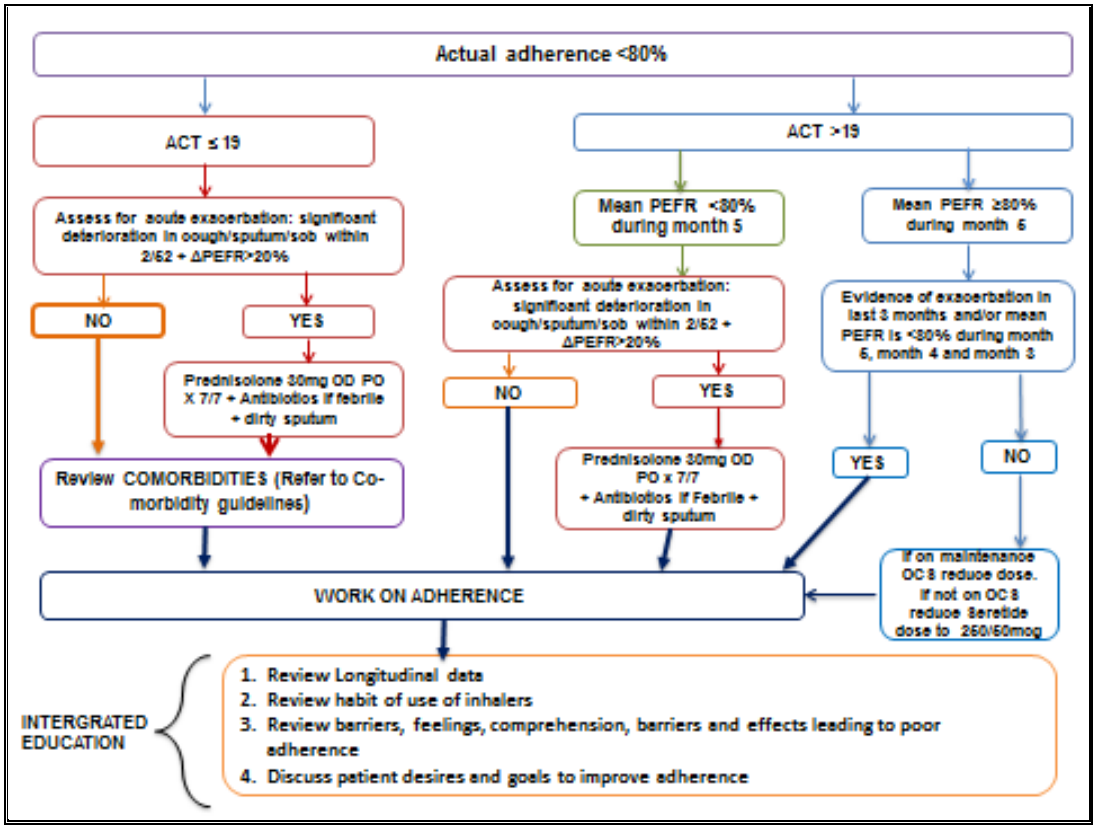


Figure 3-14 Visit 5 physician script for active group (actual adherence <80%)

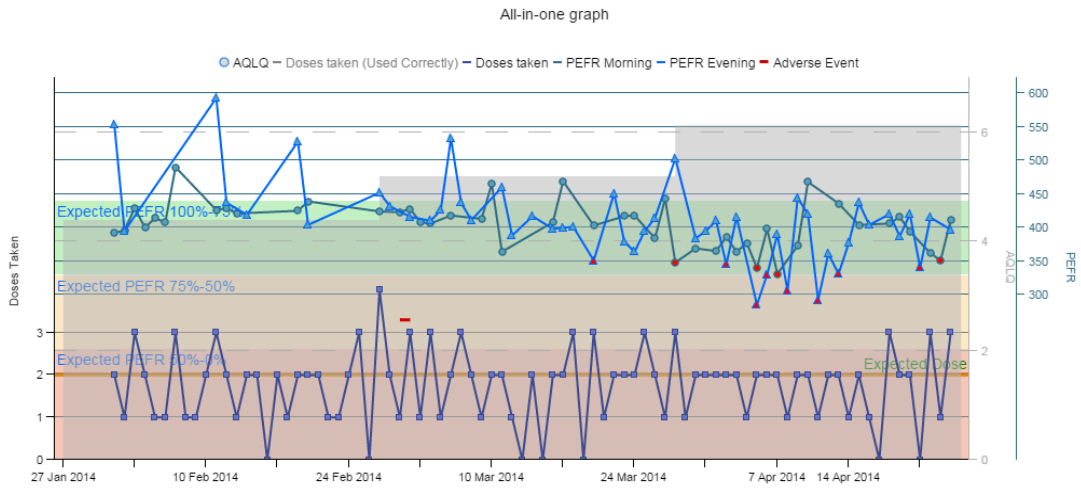


Figure 3-15 Longitudinal data actual adherence <80%

Figure 3-15 shows electronic peak flow data on the top graph and inhaler use on the bottom graph for a patient with adherence <80%.

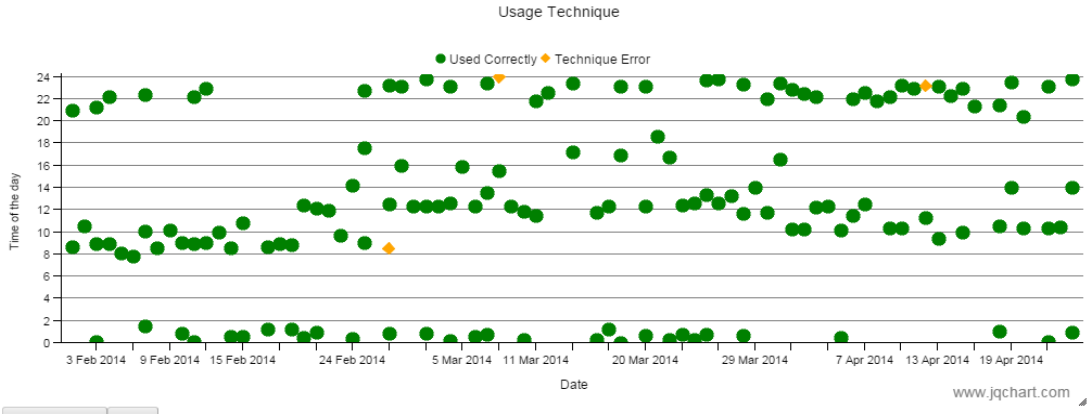


Figure 3-16 Habit of use for a patient with actual adherence <80%

Figure 3-16 shows a graph illustrating patients' inhaler use during a 3-month period. On the x-axis is date the inhaler was used and the y-axis is the time of the day the inhaler was used by the patient.

Using Figure 3-15 and Figure 3-16the physician used the longitudinal data advising a patient with actual adherence of <80% to 'WORK ON ADHERENCE'. The physician provided inhaler education as follows:

*"*You attended for your three study visits and you received inhaler education and training from the study nurse. For the three months duration you took your inhaler every day. Well done. However, most of the time you were taking your inhaler either once a day or three times a day. If you take your inhaler once per day, there is not enough medication in your body to keep your lungs stable. It is very important that you only take your inhaler twice a day as prescribed. Your peak flow is not stable, and it has dropped down in the last two months and during this time you had an asthma attack (illustrated by the red triangles and circles in the peak flow graph) In order to prevent this from happening you need to be taking your inhaler consistently twice a day.

The physician will then ask the patient if there were any reasons why the patient was not taking the Seretide inhaler twice a day and why the patient took the inhaler three times a day (addressing under dosing and overdosing). The patient usually came up with reasons why they were not adherent to Seretide inhaler, but some patients had to be prompted using the following possible reasons:

- Emotional barriers/Feelings; limited confidence in managing disease, lack of motivation.
- Social barriers; out of routine (holidays, college and doing shift work).
- Comprehension: Lack of understanding disease, inadequate understanding of the need of taking medication e.g. anxious about disease control and hence overdosing
- Discuss the patients' desires and goals to improve adherence (review goals completed during the nurses visit).

At study visit 5, if the patient's actual adherence was ≥ 80% there were three categories:

Category 1: actual adherence ≥ 80%, ACT ≤ 19, mean PEFR ≥80% (Figure 3-17)

Category 2: actual adherence ≥80%, ACT >19 OR ACT ≤ 19 PEFR<80% (Figure 3-18)

Category 3: actual adherence ≥80%: ACT >19, PEFR ≥80% (Figure 3-19)

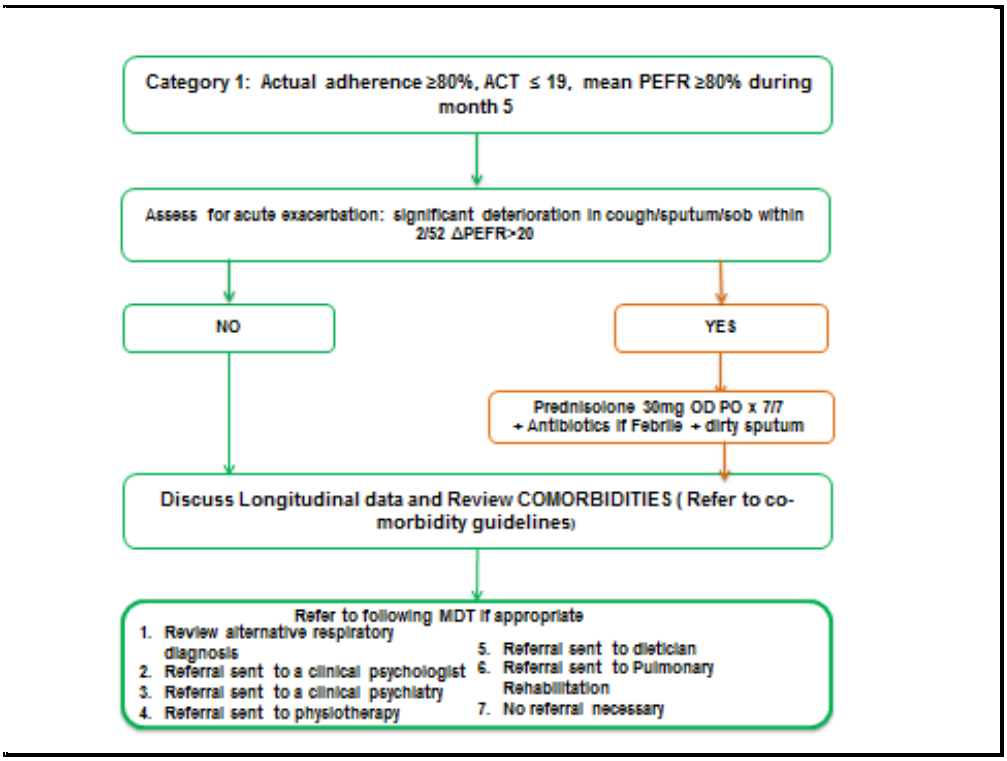


Figure 3-17 Visit 5 physician script: actual adherence ≥ 80%, ACT ≤ 19, mean PEFR ≥80%

For a patient in category 1 (actual adherence of actual adherence ≥ 80%, ACT ≤ 19, mean PEFR ≥80-Figure 3-17), the following steps were followed;

1. An assessment of an acute exacerbation was done, and the patient was prescribed a course of oral prednisolone 30mg daily for a week. After assessing for an acute asthma exacerbation inhaler education was offered using longitudinal data from the INCA device.

2. Co-morbidities were also reviewed and addressed as per the co-morbidity guideline (Figure 3-6).

3. Multidisciplinary team referral involving specialties such as psychiatry, psychology physiotherapy, pulmonary rehabilitation, dietetics as well as reviewing alternative respiratory diagnosis were conducted as appropriate. The study visit was completed, and the next physician study visit will be scheduled for the subsequent three months.

If a patient was in category 2 (Figure 3-18) steps 1 to 4 above were followed. In addition, assessment of fixed airflow obstruction done, and patient would be prescribed LAMA therapy. Furthermore, if the patient was on a lower dose of salmeterol/fluticasone (50/250mcg) the dose was increased to 50/500mcg.

If patient was in category 3 (Figure 3-19), steps 2 and 4 (above-scenario 1) were followed. In addition, patients with evidence of fixed airflow obstruction were prescribed LAMA therapy. Furthermore, if the patient was on a lower dose of salmeterol/fluticasone (50/250mcg) the dose was increased to 50/500mcg.

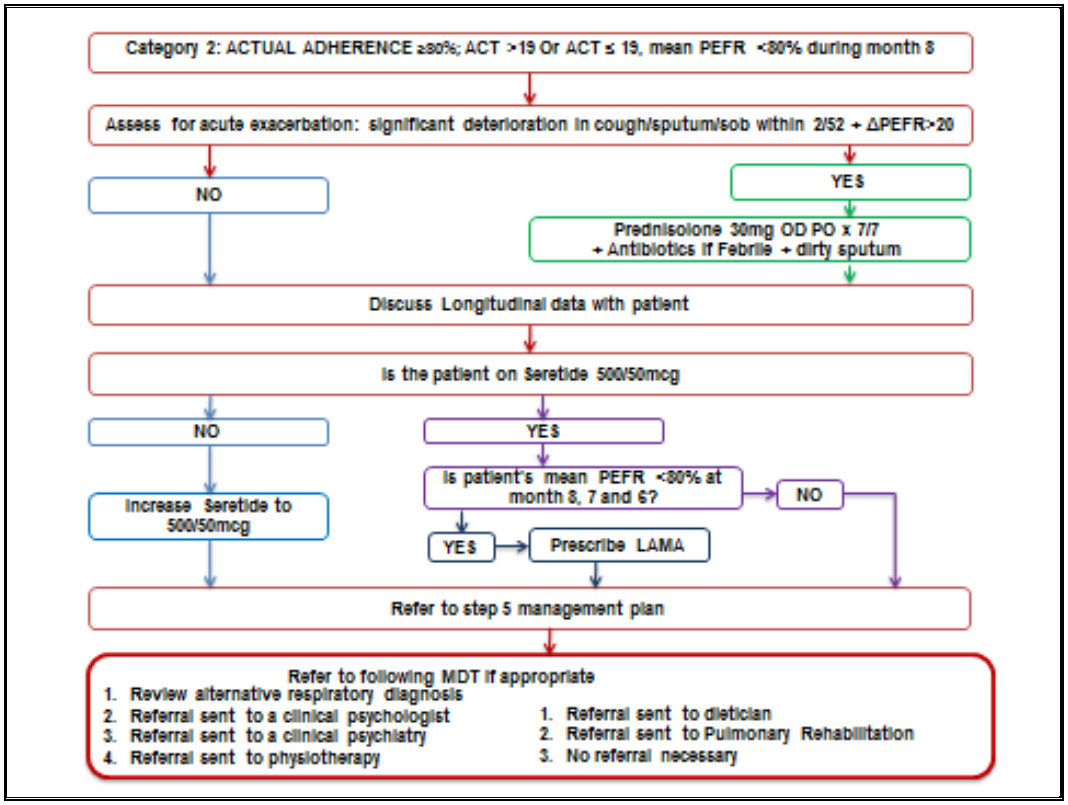


Figure 3-18 Visit 5 physician script: actual adherence ≥80%, ACT >19 OR ACT ≤ 19 PEFR<80%)

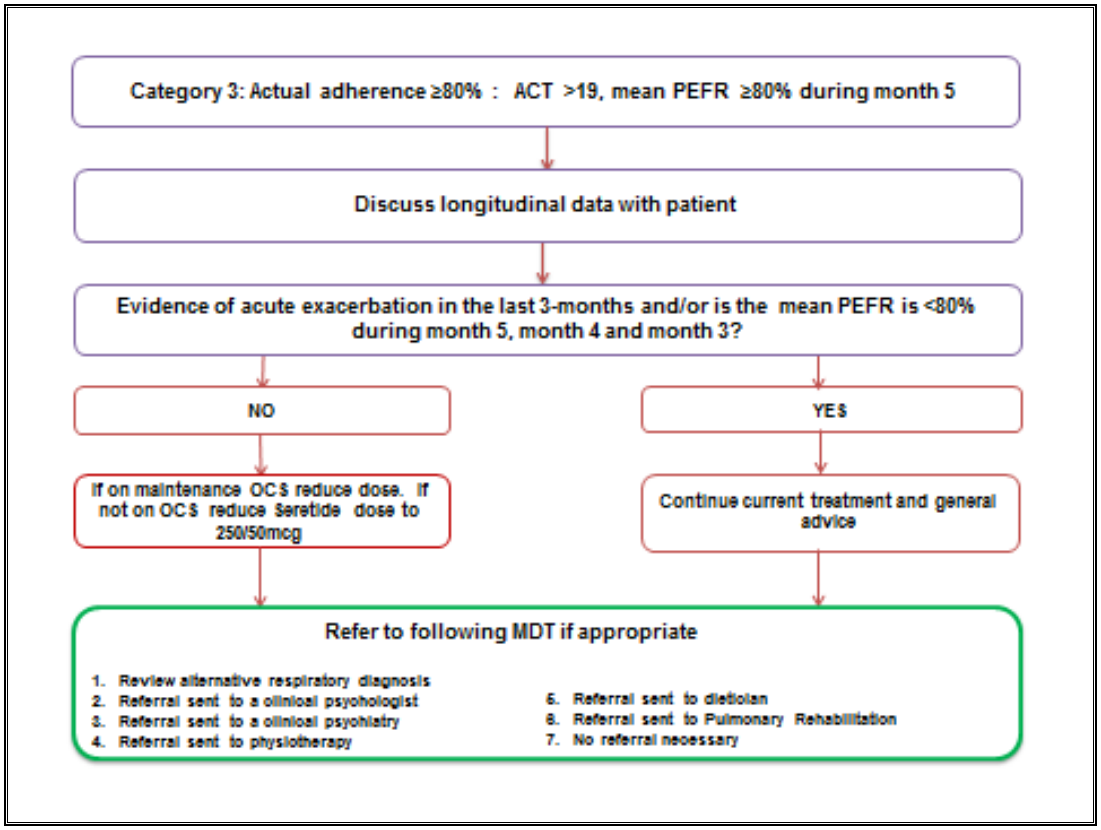


Figure 3-19 Visit 5 physician script: actual adherence ≥80%: ACT >19, PEFR ≥80%

3.3.13.6 *Visit 6 Active group*

There were four scenarios that could be followed at study visit 6:

Scenario 1: A patient with actual adherence of <80% at the study visit 6 (Figure 3-20);

Scenario 2: A patient with actual adherence of ≥80%; ACT ≤ 19 and mean PEFR ≥80% at the study visit 6 (Figure 3-21)

Scenario 3: A patient with actual adherence of ≥80%; ACT >19 OR ACT ≤ 19: and mean PEFR <80% at the study visit 6 (Figure 3-22)

Scenario 4: A patient with actual adherence ≥80%; ACT >19 and mean PEFR ≥80% at the study visit 6 (Figure 3-23).

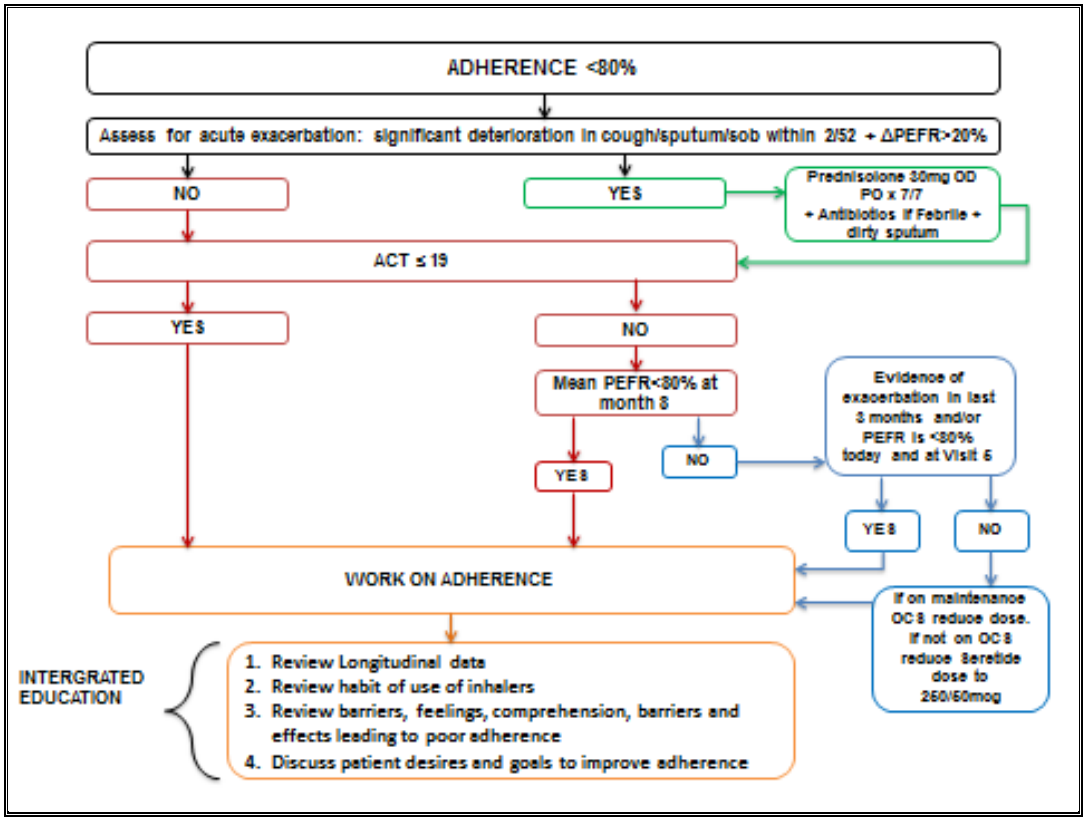


Figure 3-20 Visit 6 physician script for active group (scenario 1- actual adherence <80%)

If the patient's adherence rate was less than 80% (scenario 1) the following steps were followed:

1. Assessment of acute exacerbation of asthma was done. An acute exacerbation was defined by a significant deterioration in cough, sputum, dyspnea within a 2-week period associated with a change in PEFR of ≥20%. If an acute exacerbation was confirmed, patient was commenced on a 7-day course of prednisolone and antibiotics prescription was added if the patient was febrile and reported production of purulent sputum;
2. Assessment of asthma control using ACT was conducted. If ACT was ≤19 or >19 the emphasis was to work on improving adherence because the actual adherence rate was less than 80%. This included reviewing longitudinal data from the INCA device and electronic PEFR data and then a shared decision was made with the patient to help improve adherence to salmeterol/fluticasone propionate inhaler. In patients with an ACT>19 and a mean PEFR of ≥80% of personal best at month 8, with the absence of fixed

airflow obstruction or no exacerbations in the previous three months the dose of salmeterol/fluticasone propionate was decreased from 500 to 250mcg. If a patient was on oral prednisolone, the dose of prednisolone was decreased;

3. Inhaler education was provided by using INCA adherence data. Patients were advised to 'WORK ON ADHERENCE' as shown in Figure 3-24 and Figure 3-25.

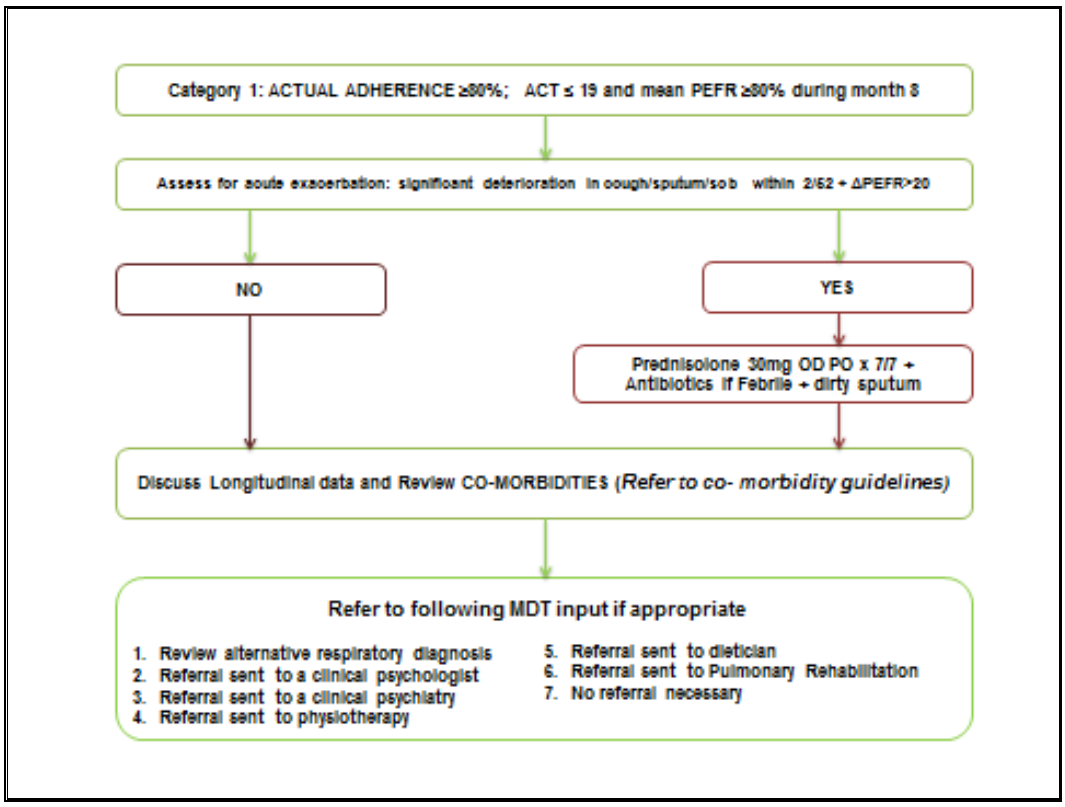


Figure 3-21 Visit 6 physician script for active group (scenario 2-actual adherence ≥80%; ACT ≤ 19 and mean PEFR ≥80%)

If the patient's actual adherence of ≥80%; ACT ≤ 19 and mean PEFR ≥80% at the study visit 6 (scenario 2) the following steps were followed:

1. An assessment of an acute exacerbation was done, and the patient was prescribed a course of oral prednisolone 30mg daily for a week. Antibiotics were prescribed if the patient reported pyrexia and purulent sputum.

2. After assessing for an acute asthma exacerbation inhaler education was offered using longitudinal data from the INCA device.

3. Co-morbidities were also reviewed and addressed as per the co-morbidity guideline (**Error! Reference source not found.**).

4. Multidisciplinary team referral involving specialties such as psychiatry, psychology physiotherapy, pulmonary rehabilitation, dietetics as well as reviewing alternative respiratory diagnosis were conducted as appropriate. The study visit was completed, and the physician would complete the study completion form. Patient was then followed up by their primary respiratory physician.

If the patient's actual adherence with actual adherence of ≥80%; ACT >19 OR ACT ≤ 19: and mean PEFR <80% at visit 6 (scenario 3/**Error! Reference source not found.**) the following steps 1, 2 and 4 under scenario 2 above were followed. In addition, salmeterol/fluticasone (50/250mcg) dose was increased to 50/500mcg. Furthermore, patients with evidence of fixed airflow obstruction were prescribed LAMA therapy. Patients who were adherent to fluticasone/salmeterol 50/500 (actual adherence of ≥80%) but had uncontrolled asthma (ACT ≤ 19) with a mean PEFR <80% at the study visit 6 (despite being on LAMA therapy) would be referred for biologic therapy (**Error! Reference source not found.**).

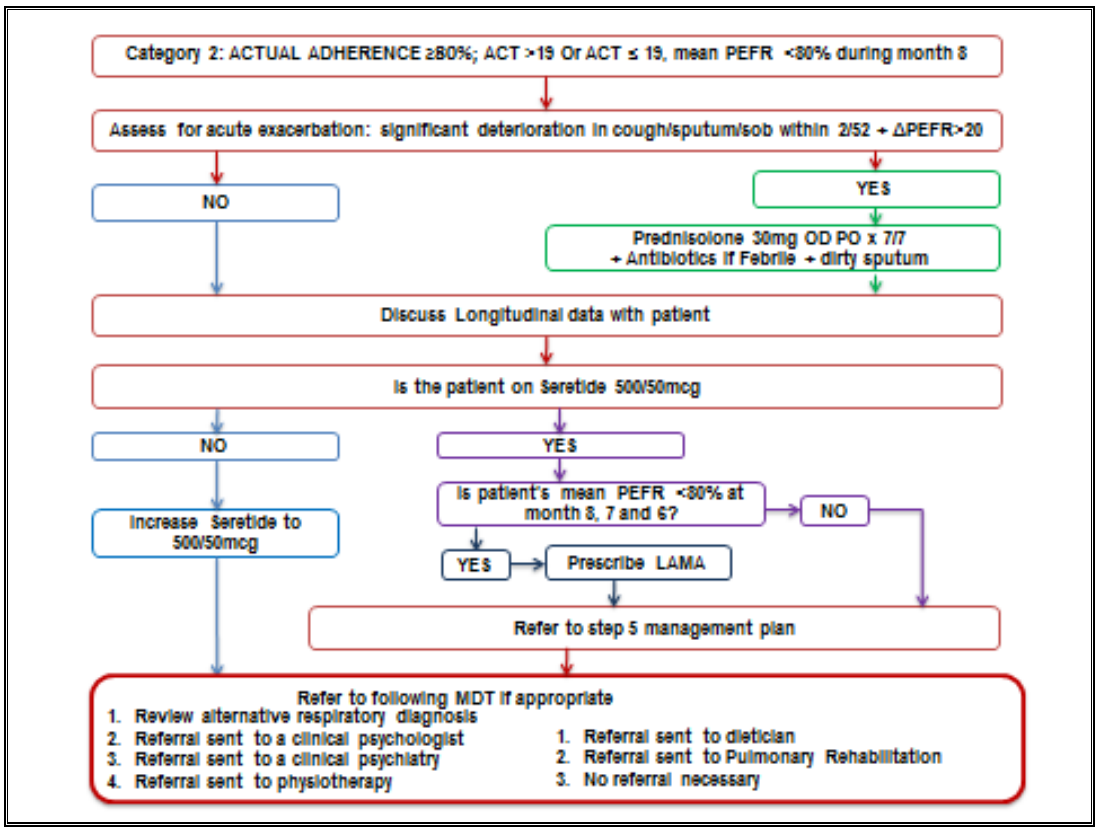


Figure 3-22 Visit 6 physician script for active group (scenario 3: actual adherence ≥80%; ACT >19 Or ACT ≤ 19, mean PEFR <80%)

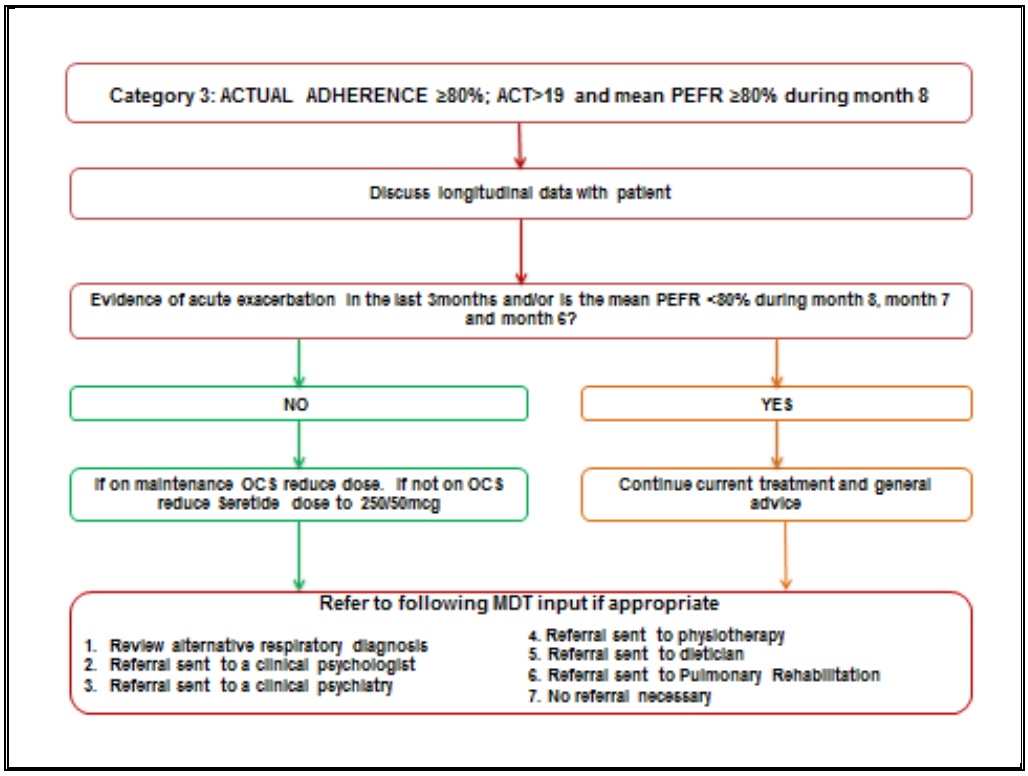


Figure 3-23 Visit 6 physician script for active group (scenario 4: Actual adherence ≥80%; ACT >19 and mean PEFR ≥80%)

If patient had actual adherence ≥80%; ACT >19 and mean PEFR ≥80% at the study visit 6 scenario 4/**Error! Reference source not found.** the following steps were followed;

1. Inhaler education was provided by using INCA adherence data. Patients were advised to 'WORK ON ADHERENCE' as shown in Figure 3-24 and Figure 3-25.
2. Exacerbation history for the previous 3 months and PEFR data for the previous three months (6,7 and 8) were reviewed.
3. If the patient had no exacerbations in the prior three months OR the PEFR was more than 80% of patients' personal best at month 6, 7 and 8 the salmeterol/fluticasone 50/500mcg dose could be reduced to 50/250mcg. Prednisolone was tapered first in patients who were on maintenance prednisolone (Figure 3-2). If the patient had an exacerbation in the prior

three months OR the PEFR was less than 80% of patients' personal best at month 6, 7 and 8 medications were not adjusted. General advice on trigger avoidance and regular exercise was offered to the patient. The study visit would end, and study completion form was completed by the investigator.

Error! Reference source not found. and Figure 3-25 illustrates how to use the longitudinal data to 'WORK ON ADHERENCE' using integrated education pathway for a patient with actual adherence of ≥80%.

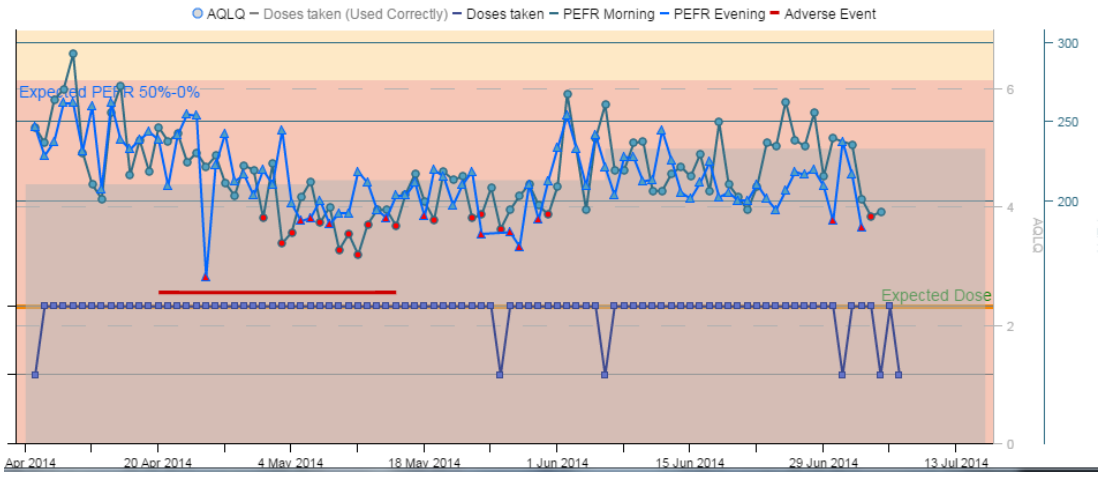


Figure 3-24 Longitudinal data actual adherence ≥80%

Figure 3-24 shows electronic peak flow data on the top graph and inhaler use on the bottom graph for a patient with adherence ≥80%

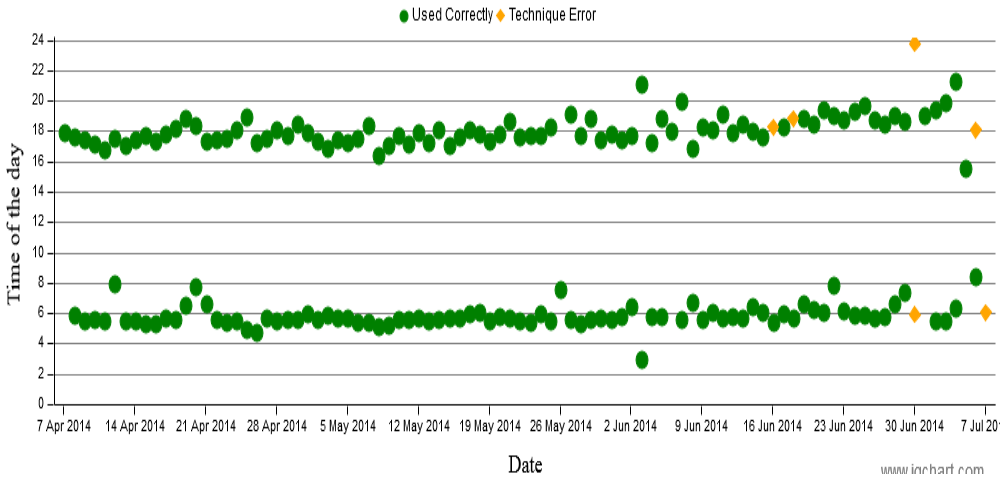


Figure 3-25 Habit of use for a patient with adherence ≥80%

Using **Error! Reference source not found.** and Figure 3-25 the physician used the longitudinal data advising a patient with actual adherence of ≥80% to 'WORK ON ADHERENCE'. The physician provided inhaler education as follows:

*"*After enrolment into the study, you attended for three study visits and you received inhaler education and training from the study nurse. During this time your inhaler use was very good; your timings were perfect, and you were taking your inhaler twice a day. Well done. The INCA Device has picked up some inhaler technique errors in the last month. When taking your inhaler, you are not taking a big enough breath in to get the drug into your lungs. You need to fully breath out, emptying your lungs before taking your inhaler. The study nurse would have gone through how to correct this error. You also had an asthma attack during the first month which took a while to resolve. Despite taking your inhaler correctly your peak flow is persistently low, (red zone) and not stable and that is why you are not feeling great. I know that you are taking your inhaler correctly but you are still unwell so I will now go through your medications to optimise your asthma control".

3.3.14 STUDY INTERVENTIONS

Patients attended six visits in total over a 32-week period (see **Error! Reference source not found.**).

3.3.14.1 *Control group: Behavioural intervention and inhaler training*

The control group were offered current best practice, which comprised of adherence optimisation, asthma education, and written action plans. The Inhaler Proficiency checklist (Figure 3-5) was used to review and correct errors in inhaler technique. At each visit consultation, a review of participant identified goals for outcomes, exploration of barriers to achieving goals, explanation of the purpose of asthma treatment and provision of an asthma management plan was conducted. At visits 4, 5 and 6, a physician reviewed the patients. The ACT scores and PEFR data taken during the previous visits was used to optimise patient treatment based on the designed physician script as detailed in Figure 3-4, Figure 3-7 to Figure 3-9 and Figure 3-11.

3.3.14.2 *Active group: Feedback using recordings from the INCA device*

In the active intervention group, inhaler education during the visits involved feedback on habit of use and inhaler technique analysis from the INCA device (based on the analysis of the data presented in a graphical format, time of inhaler use, patterns of inhaler use and inhaler technique) (297) to enhance patient's adherence and guide further treatment. A review of participant identified goals for outcomes, exploration of barriers to achieving goals, explanation of the purpose of asthma treatment and provision of an asthma management plan was also conducted. At visits 4, 5 and 6, a physician reviewed the adherence data, electronic PEFR, ACT, clinical data and used this information to optimise patient treatment based on the designed physician script (Figure 3-12 to Figure 3-14 and Figure 3-17 to Figure 3-23).

Table 3-1 Study procedures

Visit 1 (day 0): Screening visit; Visit 2 (week 1): Nurse visit; Visit 3 (week 4): Nurse visit; Visit 4 (week 8): Physician and nurse visit; Visit 5 (week 20): Physician and nurse visit; Visit 6 (week 32): Final visit; Physician and nurse visit.

Visit Number **Visit Type** **Timeline** *Study Procedures*	**Visit 1** **Nurse** **Day 0**	**Visit 2** **Nurse** **Week 1**	**Visit 3** **Nurse** **Week 4**	**Visit 4** **Nurse & Physician** **Week 8**	**Visit 5** **Nurse & Physician** **Week 20**	**Visit 6** **Nurse & Physician** **Week 32**
Informed Consent	**X**					
Inclusion/Exclusion Criteria	**X**					
Randomisation		**X**				
Demographics	**X**					
Medical/ Asthma History	**X**					
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**
Physician review				**X**	**X**	**X**
Weight and Height	**X**					

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Visit Type	Nurse	Nurse	Nurse	Nurse & Physician	Nurse & Physician	Nurse & Physician
Timeline	Day 0	Week 1	Week 4	Week 8	Week 20	Week 32
Study Procedures						
Bloods: IgE	X					
Bloods: RAST IgE	X					
Bloods: PAXgene	X					X
Bloods: Eosinophil count & Periostin	X	X	X	X	X	X
FeNO	X	X	X	X	X	X
Dispense Home FeNO monitor	X					
Retrieve Home FeNO monitor		X				
Dispense Fluticasone with INCAdevice	X					
Retrieve Fluticasone with INCAdevice		X				
PEFR	X	X	X	X	X	X
Spirometry	X		X	X	X	X
AQLQ, ACT & EQ 5D 3L	X		X	X	X	X
WPAI (Asthma)	X	X	X	X	X	X

Visit Number **Visit Type** **Timeline** *Study Procedures*	**Visit 1** **Nurse** **Day 0**	**Visit 2** **Nurse** **Week 1**	**Visit 3** **Nurse** **Week 4**	**Visit 4** **Nurse & Physician** **Week 8**	**Visit 5** **Nurse & Physician** **Week 20**	**Visit 6** **Nurse & Physician** **Week 32**
Dispense Peak flow meter	**X**	**X**	**X**	**X**	**X**	**X**
Perform IPS (Visit 1 in both groups, Visit 4 Control only)	**X**			**X**		
Review peak flow readings (Active Only)		**X**	**X**	**X**	**X**	**X**
Dispense INCA with salmeterol/fluticasone	**X**		**X**	**X**	**X**	
Dispense INCA with Salbutamol (if required)	**X**	**X**	**X**	**X**	**X**	
INCA™ download & feedback (Active only)		**X** *(fluticasone)*	**X**	**X**	**X**	**X**
Record any adverse events		**X**	**X**	**X**	**X**	**X**
Exacerbations & healthcare utilization	**X**	**X**	**X**	**X**	**X**	**X**
Asthma management plan		**X**	**X**	**X**	**X**	**X**

Visit Number **Visit Type** **Timeline** *Study Procedures*	**Visit 1** **Nurse** **Day 0**	**Visit 2** **Nurse** **Week 1**	**Visit 3** **Nurse** **Week 4**	**Visit 4** **Nurse & Physician** **Week 8**	**Visit 5** **Nurse & Physician** **Week 20**	**Visit 6** **Nurse & Physician** **Week 32**
Dispense Prescription for inhaler without INCA device						**X**

3.3.15 BIOMARKERS

At each study visit, type-2 biomarkers (peripheral blood eosinophils, serum periostin and FeNO) were measured to allow composite biomarker profiling. The composite biomarker profile was then used as part of the physician to guide step-up therapy.

3.3.16 OBJECTIVE MEASUREMENT OF INHALER ADHERENCE AND TECHNIQUE

The design, validation, and derivation of an automated algorithm and clinical use of the INCA device have all been reported. The INCA audio recordings have also been analysed for precision and accuracy in detecting inhaler technique errors (237, 240, 298-300). At the end of each month, the audio files saved on the INCA device were downloaded off the device and uploaded onto a secure web server. Within the web server is an automated algorithm that analyses each audio and provides information on critical inhaler errors. The algorithm also gives information on the date and time of each recorded inhaler use. The algorithm also gives information on the inhaler technique, particularly critical inhaler technique errors. The critical errors that can be detected include: whether the device was primed; whether the patient exhaled after priming but before inhalation; and whether there was an adequate flow (<35 L/min) (301). Therefore, the attempted and actual adherence can be calculated. The “attempted adherence” refers to the intentional initiation of medication use at the correct time. The technique adherence was defined as episodes of inhaler use in which the user made an error that critically affected medication delivery (236, 238, 240, 242, 301, 302). The actual adherence is the proportion of observed accumulation, account for both varying intervals between use and correct technique relative to expected drug accumulation if adherence and technique were perfect. This method of calculating adherence has been demonstrated to be superior to other published methods of estimating adherence for patients with both asthma and COPD (244).

3.4 STATISTICAL ANALYSIS PLAN

I prepared the statistical plan with two expert statisticians and a clinician.

3.4.1 Determination of sample size for the primary outcomes

The total sample size calculation was based on the two primary outcomes. A sample of at least 112 patients per treatment group (a total of 224) was required.

3.4.1.1 *¢ K Ŝ LJNJ⊇LJ⊇NJű ƛ ⊇ y˝ ⊇ Ŧ LJ l· ű ƛ Ŝ y˝ ű ă ø K ⊇ NJŜ Ŏ Ŝ ƛ Ȼ medication prescriptions*

Based on our previous study (82) it was anticipated that the difference in the proportion of patients who need step-up therapy in the active group would be 10% versus 30% in the control group (a difference of 20%). I then estimated that a sample size of 164 (82 per group) would provide a power of 90% at a significance level of 0.05 and with an anticipated 10% drop out rate to detect a difference of 20% between the groups.

3.4.1.2 *Mean adherence over the last 12 weeks of the study*

For the second primary outcome, I anticipated that the baseline (visit 1-2) mean adherence would be 0.65 with a standard deviation of 0.20. I also anticipated a mean {standard deviation (SD)} change from baseline to end of therapy in the INCA active group of 0.15 (0.02) and 0.05 (0.03) in the control group, a 0.10 difference. Using a two-sided alpha of 0.05, I estimated that 112 patients per treatment group (total: 224) would provide 80% power to detect a treatment difference of 0.10, assuming a combined SD of 0.25 and a 10% drop out rate.

3.4.2 Sample size calculations for the secondary outcomes

Additional sample size calculations were conducted for the secondary outcomes such as AQLQ, ACT, the annual cost for treating severe ‘refractory’ asthma individual and PEFR.

Sample size for AQLQ difference: One hundred and sixty patients per treatment group provides an estimated 80% power to detect a clinically meaningful treatment difference of 0.5 for the secondary endpoint (change from baseline in AQLQ score

over 12 weeks) by using a two-sided t-test and assuming an SD of 1.5 and a 10% dropout rate.

The sample size for ACT difference: Seventy-four patients per treatment group provides an estimated 90% power to detect a minimal clinically important difference of 3 points (253), by using a two-sided t-test and assuming an SD of 5.3 and a dropout rate of 10%.

The sample size for cost: Assuming a cost of Severe 'refractory' asthma of €4,000 (SD 2000) per annum and for others €2000 (SD 2000) and estimating to see a cost difference between active and control of €1000 per annum an estimated sample size of 80 in each group would be required.

The sample size for PEFR AUC difference: Eighty-two patients per treatment group provides an estimated 80% power to detect a treatment difference of 8% in PEFR by using a two-sided t-test, assuming an SD of 17.3 and dropout rate of 10%.

3.4.3 Description of statistical methods

The data analysis and reporting proceeded according to CONSORT guidelines for randomised controlled trials (303). The statistical analysis code is shown in Appendix 12.

3.4.3.1 *Demographic and Baseline Characteristics*

Descriptive statistics were used to describe recruited individuals and to investigate comparability of the trial arms at baseline. The number of patients and percentage was presented for categorical variables. For continuous variables that are normally distributed, the mean and standard deviation (SD) are presented.

3.4.3.2 *Primary Endpoints*

The study has two co-primary endpoints. The first co-primary endpoint was the between-group difference in appropriate asthma medication prescription at the end of the study. Appropriate medication therapy was defined as therapy after two GINA recommended cycles of review and medication changes with prior knowledge of adherence. The other co-primary endpoint was the maintenance of actual adherence (defined as the combination of the time of use, the interval between

doses and critical errors) which was calculated as a ratio of expected drug accumulation if adherence had been perfect to what was taken) (221, 304). This was assessed by the between-group (active and control) difference in the mean of actual adherence to twice daily salmeterol/fluticasone use over the last 12 weeks of the study. To compare the proportion of patients between control and active group prescribed 'inappropriate' medication (appropriate refers to GINA suggested medication changes) at the end of the study, a logistic regression model, adjusted for stratification variables, with results presented as odds ratios, 95% confidence intervals and p-values, was used.

- To compare actual adherence (reported previously(83, 221, 299, 304)), over the last 12 weeks of the study between the two groups. The actual adherence analysis would be adjusted for stratification variables {site and fractional exhaled nitric oxide (FeNO) suppression} the primary analysis would be conducted. A linear regression model, with results presented as the difference in means, 95% confidence intervals and p-values, was used. Further adjustments were conducted for any variables displaying a marked imbalance between the two groups at baseline.
  A table of primary and secondary outcomes is shown in **Error! Reference source not found.**.

Table 3-2 Primary and secondary outcomes

INhaler Compliance Assessment (INCA), Asthma Control Test (ACT), Asthma Quality of Life Questionnaire (AQLQ), European Quality of life, 5 dimensions, 3 layers (EQ-5D-3L), Work Productivity and Activity Impairment-Asthma (WPAI-Asthma) and Peak Expiratory Flow Rate (PEFR), Fractional Exhaled Nitric Oxide (FeNO)

Primary outcomes
A comparison of the proportion of patients with 'inappropriate' asthma medication prescriptions in the control group versus the active group.
A comparison of the long-term adherence rate (assessed over the last 12 weeks of the study) between the INCA /active group and the usual care group.
Secondary outcomes
To compare the ACT, AQLQ scores, EQ-5D-3L scores, WPAI-Asthma scores and PEFR rates between the active and control groups.
To compare the proportion of patients reaching stated clinical goals between the active and control groups.
To examine and compare the proportion of patients reaching stated clinical goals between the active and control groups.
To compare the proportion of patients who are 'refractory', defined as having actual adherence ≥80%, ≥1 exacerbation, PEFR am/pm <80% and ACT ≤19.
To compare the proportion of patients who are non-adherent and remain uncontrolled, i.e. Actual Adherence <80%, PEFR am/pm <80% and ACT≤19.
To compare the average time lost to work between the active and control groups
To compare the time to first exacerbation (defined by ≥20% fall in PEFR and at least doubling of reliever use for 3 consecutive days or prescribed rescue oral steroid) between the active and control groups.
To compare the proportion of patients with inhaler related side effects including oral candidiasis between the active and control groups.
To compare changes in blood eosinophil's, periostin and FeNO between the active and control groups.
To investigate the relationship of biomarker changes in relation to adherence.
To compare the proportion of patients who were clinically stable (i.e. proportion of patients who required no daily reliever use in the month prior to study end) between the active and control groups.
To investigate the relationship between changes in FeNO (characterised into FeNo>45ppb or FeNO<45ppb) and adherence.
To investigate the relationship between 7-day FeNO suppression and clinical and biomarker outcomes.
A cost-effectiveness and cost-utility analysis of the INCA educational intervention compared to the control arm would be performed.
An economic evaluation of the national implementation of the INCA-SUN program would be conducted (budget impact analysis).
To compare the average time lost to work between the active and control groups.

3.4.3.3 *Secondary endpoints*

For the following outcomes, the statistical methods described below will be conducted at the end of study completion.

An economic evaluation of the national implementation of the INCA-SUN program would be provided. Data on the cost of the intervention (device, time taken to deliver, cost of training and salary cost of the trainer), medication costs, quality of life, exacerbations and other health care utilization and associated costs, such as unscheduled health care visits as well as work productivity losses will be collected during the 32-week study. The outcome measures would be the incremental cost per exacerbation prevented and incremental cost per Quality Adjusted Life-Year (QALY). The number of exacerbations (classified as mild, moderate to severe) and time to first exacerbation would be compared between the active and the control groups over the 32-week study. In this study an exacerbation is defined as increases in symptoms i.e. cough sputum production and breathlessness within two weeks, in combination with a drop in PEFR of ≥20%. Moderate to severe asthma exacerbations are defined by prescribed rescue oral steroid, or admission to hospital, or emergency department attendance or GP visitation with an asthma exacerbation. Mild asthma exacerbation was defined as the rate of salbutamol reliever use associated with a PEFR of 60% to 80% (predicted of personal best) when not associated with a moderate or severe exacerbation or significant unscheduled hospitalisation o GP visitation. Spirometry lung function values collected at each study visit would be compared between the two study groups. Quality of life (QoL), as assessed by the AQLQ and EQ-5D-3L scores would be compared among the study groups over the 32-week study period. The WPAI-asthma scores would be compared among the two groups.

3.4.3.4 *Longitudinaldisease modelling.*

Employing multi-level survival analysis on the course of asthma over time an assessment of the interaction of predictors including adherence, FeNO, blood

biomarkers (peripheral blood eosinophils, periostin), symptoms and lung function and events (dependents) such as exacerbations in a continuous time domain will be conducted.

3.4.3.5 *Cost-effectiveness analysis*

A cost-effectiveness and cost-utility analysis of the active compared to the control arm would be performed. Incremental cost-effectiveness ratios (ICERs) would be calculated to estimate how much additional cost is required for an additional unit of benefit. A cost-utility analysis with quality-adjusted life years gained (QALYs) as effectiveness outcome (to allow for across disease comparisons) supplemented by a secondary cost-effectiveness analysis with all treated exacerbations as effectiveness outcome would be evaluated.

3.4.3.6 *Perspective*

The proposed economic evaluation would adopt an Irish publicly funded health perspective (including all substantial direct medical costs incurred in the treatment of the participants as recommended by the Irish Health Information and Quality Authority (HIQA)) as well as a societal perspective (also including indirect costs such as work productivity losses).

3.4.3.7 *Time horizon*

A 32 weeks' time horizon would be used, corresponding to the trial length. However, we anticipate that the time horizon is limited since it is less than one year and, hence, the impact of seasonal influences would not be assessed. As such, costs and effects may be impacted beyond the 32- week time horizon. Therefore, an economic modelling, based on an established Asthma Markov model, may be used to assess the cost-effectiveness over a ten-year time horizon (305).

3.4.3.8 *Resource use measurement, valuation and costs*

The main areas of resource use to be collected are: (i) health care utilisation, (ii) medication costs and (iii) costs associated with the INCA intervention. Health care utilisation data were collected on (i) numbers of GP visits, (ii) number and duration of Emergency department attendance and (iii) number, duration and reason for hospital admissions (if any). Medication costs would be collected including details

of dose, frequency and type of medications use and the duration of medication use. Information on concomitant medications was also recorded, but information on costs, unless directly related, would not be included. The time for delivering the intervention and device cost was recorded as part of the study protocol. The differential costs associated with managing patients in the two arms of the trial would be estimated from data from the trial and unit costs available from the participating hospitals. GP visits cost between approximately €50 and €70 per visit (306). Days in the hospital would be costed using the average cost per patient per day based on Drug-Related Group (DRG) case-mix costs. These costs include all resources used during the hospital stay. Drug costs would be available via MIMS or costs for reimbursable items under the community drug schemes. Time for delivering the intervention would be costed using HSE salary scales at the time of the study, including PRSI.

3.4.3.9 *Outcomes*

Asthma-specific and general quality of life would be assessed using the AQLQ and EQ-5D-3L respectively. A utility would be derived from the EQ-5D scores using Irish valuation tariffs. It is anticipated that Irish valuation tariffs would l be available by the end of the trial. In the absence of Irish public preference data, UK tariffs would be considered. Regarding the exacerbation outcome measure, statistical modelling would be used to assess the risk of exacerbations based on factors, including adherence rates, lung function and patient identified risks during the intervention, bearing in mind the duration of the interview.

3.4.3.10 *Other Secondary endpoints*

For the remaining secondary endpoints, the analyses would l involve intention-to-treat comparisons between the two groups, with transformation as appropriate after examination of distributions and adjustment for stratification variables. All analyses would use appropriate logistic or linear regression models, with results presented as point estimates (odds ratios or difference in means), 95% confidence intervals and p-values. A further adjustment would be made for any variables displaying a marked imbalance between the arms at baseline. All final models

would undergo appropriate diagnostic testing to identify points of high influence or leverage, the adequacy of model fit and compliance with model assumptions.

To assess the time to first exacerbation (defined by 20% or more fall in PEFR and at least doubling of reliever use for three consecutive days or prescribed rescue oral steroid) a log-rank test and Cox's proportional hazards regression would be used, stratified for site and FeNO (as used in the randomisation procedure). Hazard ratios with 95% confidence interval and p-values would be reported.

3.4.3.11 *Subgroup Analysis*

This study requires that patients use a salmeterol/fluticasone inhaler. Some patients would have been already prescribed salmeterol/fluticasone inhaler, but in some patients, it would have been prescribed recently (within 6 months). Hence, subgroup analysis would be conducted by investigating only patients who have previously used a salmeterol/fluticasone inhaler and, following this, looking at those who never previously used a salmeterol/fluticasone inhaler.

3.4.4 QUALITY CHECK PLANS

An independent quality risk monitor carried monitored visits to each participating site on at least one occasion during the conduct of the study. The role of the quality risk monitor was to ensure that the study was conducted according to Good Clinical Practise guideline; ensure that the protocol was been adhered to; ensure that all pertinent information (such as signed informed consent and questionnaires) have been recorded. The quality risk monitor also performed data verification, monitored product accountability (for example fluticasone/sameterol, salbutamol drug dispensing logs) and ensured that all the CRFs were complete and were signed off by the nurses and the investigators. Another quality check would be conducted at the end of the study. The quality check would include:

- Ensuring any change to population criteria is documented.
- Checking suggested handling of data problems is appropriate.

- Checking individual inclusion/exclusion criteria correspond to the protocol deviation listings.
- The trial monitoring committee would resolve uncertainties regarding the inclusion of patient statistical analyses.
- Checking appropriateness and completeness of the proposed statistical methods and presentation of results agree with the protocol.
- Ensuring justification of any changes to planned analyses from those described in the protocol.
- Checking agreement of the details of any report with the objectives of the study.
- Checking the content of the report is appropriate and complete.

3.5 RESULTS

3.5.1 Study Participants

Between October 2015 and May 2018, 130 patients were recruited and randomised (63 allocated to the active/biofeedback group and 66 to control/standard care group) from four specialist asthma clinics in the Republic of Ireland and Northern Ireland. Of the 130 patients, 63 patients were randomised to the active (INCA-biofeedback), and 66 were randomised to the control group. Five patients (0.4%) withdrew prematurely. Of the five patients who dropped out of the study, two did not complete the study because of either work commitments or family circumstances; two patients dropped out of the study with no reasons, and one could not tolerate the Seretide. The flow of the patients through the study is shown in **Error! Reference source not found.**Figure 3-26.

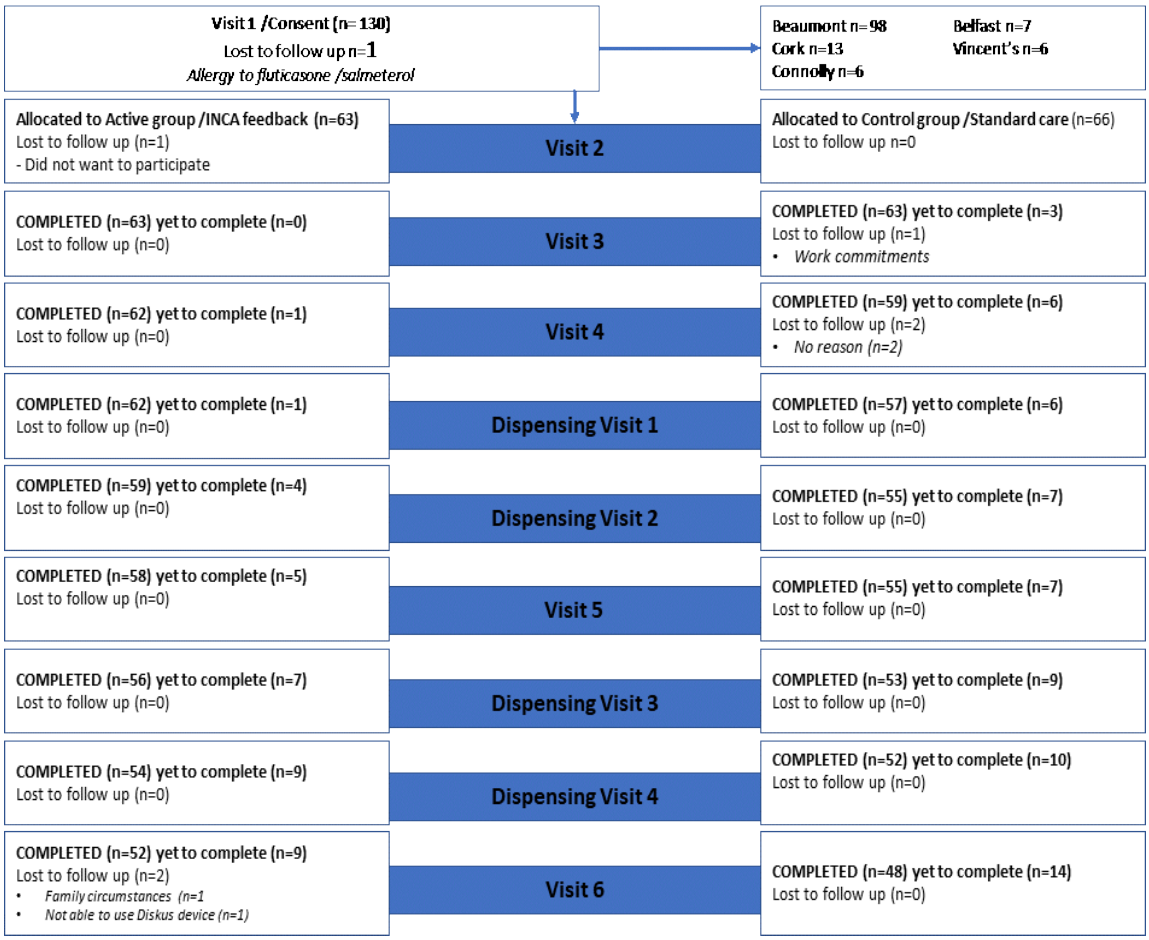


Figure 3-26 Study flow/consort

130 patients were randomised to active and control groups. Five patients were lost to follow up.

The characteristics of the recruited patients are shown in Table 3-3. Of the 130 patients recruited, 90 patients have completed the study, but data were available for 83 patients. Of the 83 patients, 56 (67.47%) were female, and 55 (66.27%) non-smokers. The average age was 48.88 ±14.09, and the mean body mass index was 29.6±7.48. The mean ACT was 12.98±3.67, the average number of exacerbations in the past year was 4.67±2.60 and the average number of oral steroid courses in the past year was 3.93±2.59 suggesting inadequate asthma control. There were no significant differences in the patient characteristics between the active and control groups at randomisation.

Table 3-3 Baseline characteristics of the recruited patients

Baseline patient characteristics for all recruited patients presented as mean ±SD unless stated otherwise. *T-tests, proportions test or chi-squared test used as appropriate.

Body Mass Index (BMI), Forced Expiratory Volume in 1 second (FEV1), Long-Acting Muscarinic Antagonist (LAMA), Asthma Quality of Life (AQLQ), Asthma Control Test (ACT), Peak Expiratory Flow Rate (PEFR)

	INCA BIOFEEDBACK GROUP	**CONTROL GROUP**	**TOTAL**	**P-VALUE***
PARTICIPANTS N (%)	41 (49.0%)	42 (50.6%)	83 (100)	
AVERAGE AGE IN YEARS **±** SD	47.71±14.17	50.02±14.08	48.88 ±14.09	0.5
AVERAGE BMI (KG/M^2) **±** SD	28.94±7.34	30.18±7.65	29.6±7.48	0.5
FEMALES N (%)	25 (60.98)	31 (73.81)	56 (67.47)	0.83
SMOKING HISTORY N (%)				
NEVER SMOKERS	23 (56.19)	32 (76.19)	55 (66.27)	0.14
EX-SMOKERS	17 (41.46)	9 (21.43)	26 (31.33)	
CURRENT SMOKER	1 (2.44)	1 (2.38)	2 (2.4)	
AVERAGE				

	INCA BIOFEEDBACK GROUP	CONTROL GROUP	TOTAL	P-VALUE*
AVERAGE BASELINE FEV_1 **IN** L **±** SD	2.55±1.02 n=32	2.51±0.91 n=39	2.53±0.96 n=71	0.84
AVERAGE BASELINE FEV_1 % PREDICTED ± SD	80.78±22.85 n=32	87.59±23.95 n=39	84.52±23.54 n=71	0.23
AVERAGE FEV_1/FVC RATIO ± SD	0.69±0.13 n=32	0.71±0.14 n=39	0.70±0.14 n=71	0.60
AVERAGE PEFR IN L/MIN ± SD	433.27±175.31	416.19±147.39	424.63±161.02	0.63
AVERAGE FENO **±** SD	22.38±18.88 n=40	26.19±26.43 n=42	24.32±22.1 n=82	0.46
SERUM EOSINOPHILS Ó 0 ,3 CELLS·ML^{-1} N (%)	14 (38.89)	19(50)	33 (44.59)	0.34
SERUM EOSINOPHILS <0.3 CELLS·ML^{-1} N (%)	22 (61.11)	19(50)	41 (55.41)	
AVERAGE NUMBER OF ORAL STEROID COURSES IN THE PAST YEAR **±** SD	4.15±2.70	3.71±2.49	3.93±2.59	0.45
AVERAGE NUMBER OF EXACERBATIONS IN THE PAST YEAR **±** SD	4.90±2.73	4.45±2.48	4.67±2.60	0.43

	INCA BIOFEEDBACK GROUP	CONTROL GROUP	TOTAL	P-VALUE*
SALMETEROL/FLUTICASONE DOSE N (%) PATIENTS				
250 ɾ G	14 (34.15)	10 (23.81)		0.3
500 ɾ G	27 (65.85)	32 (76.19)		
AVERAGE ACT **±** SD	12.68±3.46	13.26±3.88	12.98±3.67	0.48
AVERAGE AQLQ **±** SD	3.82 ±1.07 n=39	3.94±1.17 n=41	3.88±1.12 n=80	0.63
AVERAGE EQ-5D-3L **±** SD	7.46 ±1.73	7.29 ± 1.79	7.37±1.75	0.65
WPAI-ASTHMA	0.51±0.51 n=39	0.63 ± 0.49 n=38	0.57±0.50	0.3

3.6 DISCUSSION

The aim is to recruit 220 patients and conduct a full analysis of the primary and secondary outcomes. It is expected that by using the INCA adherence data, lung function and patient-related outcomes it would be possible to assess if a clinician is better equipped to optimise asthma treatment appropriately. Changes in adherence would be related to the changes in the biomarker to identify patients with 'refractory' asthma with either T2 high or low asthma. Understanding of the inflammatory biology would guide individualised further step-up therapy, identifying patients who are likely to respond to biologic therapy and those who are less likely to respond to corticosteroid therapy. Sub-group analyses of the different asthma phenotypes and investigating the relationship between the asthma phenotype, lung function, asthma exacerbations and symptoms would provide insight into the heterogeneity of 'refractory' asthma.

3.6.1 Limitations

The study is still recruiting, and hence data cleaning is still on-going. A limitation to this study is that the control group received care which is above usual care such as education about their disease, PEF monitoring, as well as attending for eight visits over the eight-month period. This does not reflect current clinical practice and would result in improved patient-related clinical outcomes such as asthma control test, EQ-5D-3L and AQLQ scores. Another limitation of the study is that the provision of free inhalers, the frequent study visits and hence increased contact with health care providers would lead to higher adherence rates than would be seen in clinical practice and, hence, a substantial difference in the adherence rates between the INCA-biofeedback group and the control group might not be detected. The 32-week study period may be too short to demonstrate seasonal effects of asthma which may be significant in some patients.

3.7 CONCLUSION

Assessment of inhaler adherence and providing individualised inhaler adherence education is crucial in the management of patients with severe uncontrolled asthma. Identifying 'refractory' asthma and understanding the underlying asthma phenotype allows appropriate step-up therapy. In this chapter, I developed a physician script that incorporates the use of recorded lung function, asthma control screening tool (ACT), clinical history and electronically recorded INCA data to guide asthma medication adjustment. Using INCA device inhaler adherence to provide individualised inhaler education, barriers to medication adherence are addressed in this study. I recruited 130 patients of which 90 patients have completed participating in the study.

Chapter 4. CONCLUSIONS AND FUTURE DIRECTIONS

4.1 Introduction to the chapter

This project focused on the use of an inhaler as well as adherence to optimise asthma treatment in patients who continue to have symptoms and experience frequent exacerbations despite therapy with moderate to high dose inhaled corticosteroids in combination with a beta-2 agonist. Firstly, the assessment of patients classified as having severe asthma was reviewed to illustrate the significance of confirming that a patient has an actual asthma diagnosis. Furthermore, identifying the underlying cause of uncontrolled severe asthma, which could be due to non-adherence and untreated comorbidities or 'refractory' disease was discussed. I further explained the different mechanisms underlying 'refractory' asthma. I also addressed some of the different underlying reasons for non-adherence to inhaled asthma therapy. I have discussed the relationship of non-adherence and clinical outcomes as well as the significance of identifying asthma inflammatory biology in patients with 'refractory' asthma. This is critical to ensure that the available expensive biologic asthma treatment is used cost-effectively.

I then reviewed the assessment and monitoring of adherence to inhaler therapy in clinical trials of add-on therapy in severe asthma. Most of these studies included in the systematic review have been conducted in recent years assessing the effectiveness of biologic add-on therapies in patients with severe asthma. These studies have shown the significance of 'choosing the right patient for the correct drug' {reduction in asthma exacerbations in patients with high eosinophil levels for targeted anti-IL5 therapy in Reslizumab (128, 209)and Mepolizumab studies (95, 183, 307); efficacy of lebrikizumab in reducing the rate of asthma exacerbations and improving lung function in periostin-high patients' (103)}. Therefore, these therapies are expensive because of associated high drug development costs. Furthermore, conducting these clinical trials is also expensive because large samples sizes are required to achieve an effective size that would demonstrate an important treatment difference. The results of the systematic review showed that the absence of monitoring adherence to maintenance therapy during the conduct of the clinical trial account for large variances in outcome measures such as FEV1

and PEFR. Consequently, larger sample sizes are required to compensate for the large variance in the clinical outcomes. Furthermore, failure to assess adherence to ICS/LABA in the screening phase of the study risks including patients with 'difficult to treat' asthma and thus, introducing a significant additional variance with subsequent higher standard deviations in the outcomes. This also means that potentially participants recruited to these studies had suboptimal adherence to ICS/LABA therapy who would not be considered eligible for these therapies. In clinical practice, it may be undesirable to exclude patients with suboptimal adherence to maintenance asthma therapy because this would not reflect the adherence behaviours in real life. However, given the significant variance, and potential loss of power due to the absence of monitoring adherence efforts should be made to control for adherence in clinical trials of add-on therapy.

The systematic review also demonstrated that 20 trials out of 87 reported ICS/LABA adherence monitoring and none of these trials used electronic monitors. Electronic monitors such as the Propeller device (78) and MDILOg have sensors that record the date and time of each inhaler actuation and have the advantage of in-built missed doses reminders based on the patient's treatment. These monitors can be used in the clinical trials to objectively assess adherence to ICS/LBA therapy. Thus, allowing suboptimal adherence to be detected and addressed and consequently the study power may potentially be improved, and the sample size will be decreased by approximately 50%.

Using a validated adherence measure (INCA device) I designed the INCA-SUN study to assess the effect of providing individualised feedback on inhaler education and relationship to clinical outcomes. The INCA device is advantageous in assessing inhaler adherence because it assess both the habit of use of the inhaler and the technique errors that the patient makes when they take an inhaler. I designed a physician script using the inhaler adherence information to tailor adherence interventions that addresses both the underlying cause of non-adherence and correct inhaler technique. I plan to test the hypothesis that the adherence intervention that focuses on promoting a habit of use of the inhaler, address the cause of poor adherence as well as correcting the inhaler technique would lead to

improved adherence and consequently improved clinical outcomes. Using the physician script, I aim to test the hypothesis that the inhaler adherence education from the INCA device can be used to guide clinicians to make critical decisions on optimisation of asthma medication. Thus, the use of INCA device inhaler adherence may be used in clinical practise to guide clinicians in distinguishing patients with 'difficult to treat' asthma from those with 'refractory' asthma. The use of the adherence data in association with the biomarkers would allow clinicians to recognise clusters of demographic, clinical and/or pathophysiological characteristics (Th2 high and Th2 low asthma) and will ensure that appropriate treatment is prescribed to the appropriate population group and the available phenotype-guided treatment can be targeted to the particular phenotype of severe asthma patients. If the INCA device education intervention can prove to be cost-effective there will be sufficient grounds to adopt it worldwide.

4.2 Future directions

Within this project I have demonstrated that assessment of adherence to maintenance inhaled corticosteroids and beta-2 agonist therapy is rarely done in clinical trials of add-on therapy conducted in patients with severe asthma. Inhaler adherence to maintenance asthma therapy was neither monitored prior to randomisation nor during the conduct of the clinical trials. I have demonstrated that failure to assess and monitor inhaler adherence not only leads to recruiting ineligible patients with ''difficult to control' asthma' but will also introduce a higher placebo effect into subjective outcomes such as an exacerbation which are the prominent outcomes assessed in the clinical trials. I have demonstrated that the absence of not monitoring adherence to maintenance asthma treatment in the clinical trials of add-on therapy leads to higher variances and their corresponding standard deviations consequently reducing the study power and hence requiring larger sample sizes to achieve the desired treatment effect. This means that longer and more costly trials must be conducted that may be avoided by monitoring adherence to maintenance ICS/LABA therapy.

To ensure that good quality data is obtained from the clinical trials of add-on therapy it is also important to use adequate methods of measuring adherence to assess inhaler adherence. Despite the importance of inhaler adherence, there is limited data regarding how to assess inhaler adherence and real-time inhaler adherence measures that can provide feedback to the patient immediately after taking the inhaler. Nonetheless, the advent of the INCA device and its use in patients with asthma and chronic obstructive pulmonary disease has shown an important relationship between the improvement of adherence and clinical outcomes (82, 308). Future work in clinical trials of add-on therapy in severe asthma should focus on using electronic monitors such as the propeller device and INCA device to monitor adherence to ICS/LABA therapy. Objective monitoring of adherence in the screening phase will ensure that patients with 'refractory' asthma, who are eligible for add-on therapies, are recruited into the clinical trial. Objective monitoring of adherence during the conduct of the study will enable identify sub-optimal adherence and individualised adherence interventions can be implemented. Ultimately, the study costs will be reduced because the costs of the use of the electronic adherence monitors will be outweighed by the costs of running the study with a smaller sample size. One of the limitations in conducting the systematic review was the inconsistencies in reporting of clinical outcomes. For example; different definitions were used to define exacerbations and the inconsistency in reporting this outcome across the clinical trials made it difficult to conduct a meaningful meta-analysis. FEV1 was also reported inconsistently across the studies. FEV1 was reported in three different ways: the absolute change in FEV1; per cent change in absolute changes in FEV1 and change in the per cent predicted FEV1. Therefore, an effort to standardise asthma clinical outcomes such as exacerbations and lung function should be made internationally.

With the use of the INCA device, I aim to demonstrate that individualised interventions that focus on correcting inhaler technique, habit of inhaler use and

addressing the cause of poor adherence can be implemented in clinical practice. I also hope to show that electronically recorded inhaler adherence data, measured by the INCA device, can be used to identify patients who have severe uncontrolled asthma due to poor adherence and untreated co-morbidities. In these patients the focus of treatment will be to treat modifiable comorbidities and provide tailored adherence interventions. Treatment step-down can be initiated once patients achieve good adherence. By using the adherence data from the INCA device to identify patients with good adherence (≥ 80%), but 'refractory' to treatment (that is, patients who still have persisting symptoms and frequent exacerbations despite treatment of co-morbid disease. These patients can then be prescribed additional step-up therapy. I would hope that after study completion that there will be robust data to show that the use of INCA device inhaler adherence data is essential in guiding clinical decision making in the management of severe uncontrolled asthma.

Future work includes completing the Inhaler Compliance Assessment in Severe UNcontrolled (INCA-SUN) asthmatics study and examining the persistence of adherence; thus, comparing the first 12 weeks of the study and the last 12 weeks of the study. The relationship of inhaler adherence and clinical outcomes will be assessed. The cost-effectiveness and cost-utility analysis of the INCA educational intervention as well as the economic evaluation of the national implementation of the INCA-SUN program will be conducted. Future replicate studies can be conducted with a prolonged duration of the study, for example, twelve months to allow assessment of the seasonal asthma effects which will be important especially for assessment of outcomes such as exacerbations. Conducting a prospective real-life study with reduction of study visits and other modifications such as not providing the inhaler to the patient will be essential in replicated studies because adherence rates will be more reflective of the actual adherence in clinical practice.

Further work should also focus on real-time inhaler adherence feedback whereby patients will be informed immediately of the inhaler technique error and will be able to correct the inhaler technique for the next inhaler dose. Personalised inhaler

education interventions should be implemented in the real-world setting and observational studies can be conducted to assess their cost-effectiveness.

My research using the INCA device to assess inhaler adherence in the asthma population is being conducted in multiple sites. Hence, I believe after the study completion the results could be generalised to the Irish population. However, the external validity of the results in non-Irish populations can be assessed by conducting future reproducible studies. The INCA team is working currently working on INCA devices that can be used with devices other than Diskus inhaler and hence replicate studies can be conducted in the future.

There is a limited use of electronic monitors outside research/ clinical trial settings. Future work should also focus on real-life use of electronic monitors to highlight their acceptability and feasibility in real life practice. Recent work by the INCA group (82, 308) have shown the relationships of different behaviour patterns in COPD and to clinical outcomes. The use of electronic monitors in clinical practise for asthma patients may lead to increased inhaler adherence and better self-management and aid clinicians in managing severe asthma. Therefore, future work should focus on replication of studies such as the INCA-SUN study to assess how different patterns of inhaler use impact on clinical outcomes. Larger multi-site, longer-term studies would be required to determine if adherence improvements can be sustained and to assess how that relates to clinical outcomes. The use of electronic monitors in clinical practise would provide reliable patient adherence data and therefore, clinicians can make informed treatment decisions. By accurately monitoring inhaler adherence in asthma, poorly controlled patients due to sub-optimal inhaler adherence can be identified and individualised adherence interventions can be implemented rather than unnecessarily escalating treatment with expensive add-on treatment. Zafari et al. (305) has shown that an adherence program that increases adherence by 50% could be as low as US $130 per person annually to be cost-effective which are lower than the costs of unnecessarily

escalating treatment with biologic therapy. Therefore, the cost of electronic monitors may be balanced by savings made by avoiding escalation of therapy.

4.3 CONCLUDING REMARKS

Conducting this research has led to a few insights on management of patients with severe asthma. By conducting the systematic review, I have shown that objective adherence monitoring prior to enrolling patients ensures that patients with 'refractory' asthma are enrolled into the clinical trials. Adherence monitoring during the conduct of the clinical trial ensures that placebo effects are accounted for and true effect sizes will be estimated. Therefore, the cost of running a clinical trial will be reduced because the sample sizes will be smaller with satisfactory study power. I have demonstrated that a systematic evaluation of patients with severe asthma is required to identify the reasons for persisting symptoms and frequent exacerbations. I have shown that, in order to achieve the control based asthma management, it is critical to adjust pharmacological and non-pharmacological treatment in a continuous cycle that involves assessment, treatment and review of response (4). I have also shown that treating modifiable risk factors, assessment of adherence in addition to reviewing and correcting inhaler technique errors is paramount in the management of patients with severe asthma. The assessment of treatment response, aiming to decrease or escalate therapy as well as addressing patients concerns and medication adverse effects is vital to maintain optimal compliance with maintenance therapy. I have also shown that an individualised adherence intervention that addresses both the cause of non-adherence and the inhaler technique leads to improved inhaler adherence. The identification of the disease phenotype may significantly affect the choice of diagnostic tests and the long-term prognosis, and most importantly predict responsiveness to specific pharmacotherapies.

References

1. Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. The New England journal of medicine. 1991;325(6):388-92.
2. Murphy AC, Proeschal A, Brightling CE, Wardlaw AJ, Pavord I, Bradding P, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. Thorax. 2012;67(8):751-3.
3. Hyland ME, Whalley B, Jones RC, Masoli M. A qualitative study of the impact of severe asthma and its treatment showing that treatment burden is neglected in existing asthma assessment scales. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2015;24(3):631-9.
4. Global Initiative for Asthma (GINA). Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention AfwgoAS. 2018 GINA Report, Global Strategy for Asthma Management and Prevention. 2018.
5. Lucas AE, Smeenk FW, Smeele IJ, van Schayck CP. Overtreatment with inhaled corticosteroids and diagnostic problems in primary care patients, an exploratory study. Fam Pract. 2008;25(2):86-91.
6. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Asymptomatic bronchial hyperresponsiveness in rhinitis. The Journal of allergy and clinical immunology. 1985;75(5):573-7.
7. O'Byrne PM, Reddel HK, Eriksson G, Ostlund O, Peterson S, Sears MR, et al. Measuring asthma control: a comparison of three classification systems. European Respiratory Journal. 2010;36(2):269-76.
8. Pinnock H, Burton C, Campbell S, Gruffydd-Jones K, Hannon K, Hoskins G, et al. Clinical implications of the Royal College of Physicians three questions in routine asthma care: a real-life validation study. Prim Care Respir J. 2012;21(3):288-94.
9. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. The European respiratory journal. 1999;14(4):902-7.
10. Juniper EF, O'Byrne PM, Ferrie PJ, King DR, Roberts JN. Measuring asthma control. Clinic questionnaire or daily diary? American journal of respiratory and critical care medicine. 2000;162(4 Pt 1):1330-4.
11. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. The Journal of allergy and clinical immunology. 2004;113(1):59-65.
12. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. The Journal of allergy and clinical immunology. 2006;117(3):549-56.
13. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA, Gern J, et al. Asthma outcomes: Exacerbations. Journal of Allergy and Clinical Immunology. 2012;129(3):S34-S48.
14. Loymans RJ, Honkoop PJ, Termeer EH, Snoeck-Stroband JB, Assendelft WJ, Schermer TR, et al. Identifying patients at risk for severe exacerbations of asthma: development and external validation of a multivariable prediction model. Thorax. 2016;71(9):838-46.
15. Papadopoulos NG, Christodoulou I, Rohde G, Agache I, Almqvist C, Bruno A, et al. Viruses and bacteria in acute asthma exacerbations--a GA(2) LEN-DARE systematic review. Allergy. 2011;66(4):458-68.

16. Network BTSaSIG. British guideline on the management of asthma. A national clinical guideline. September 2016. brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2016/ (accessed September 2018).
17. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. The European respiratory journal. 2007;30(3):452-6.
18. Li D, German D, Lulla S, Thomas RG, Wilson SR. Prospective study of hospitalization for asthma. A preliminary risk factor model. American journal of respiratory and critical care medicine. 1995;151(3 Pt 1):647-55.
19. Kitch BT, Paltiel AD, Kuntz KM, Dockery DW, Schouten JP, Weiss ST, et al. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow-up. Chest. 2004;126(6):1875-82.
20. Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, et al. FEV(1) is associated with risk of asthma attacks in a pediatric population. The Journal of allergy and clinical immunology. 2001;107(1):61-7.
21. Osborne ML, Pedula KL, O'Hollaren M, Ettinger KM, Stibolt T, Buist AS, et al. Assessing future need for acute care in adult asthmatics: the Profile of Asthma Risk Study: a prospective health maintenance organization-based study. Chest. 2007;132(4):1151-61.
22. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. American journal of respiratory and critical care medicine. 2009;179(1):19-24.
23. Reddel HK, Jenkins CR, Marks GB, Ware SI, Xuan W, Salome CM, et al. Optimal asthma control, starting with high doses of inhaled budesonide. European Respiratory Journal. 2000;16(2):226-35.
24. Lurie A, Marsala C, Hartley S, Bouchon-Meunier B, Dusser D. Patients' perception of asthma severity. Respiratory medicine. 2007;101(10):2145-52.
25. Global Initiative for Asthma. Asthma Management and Prevention. NIH Publication number 95-3659A. Bethesda NIoH, 1995. 1995.
26. National Heart L, and Blood Institute. National Asthma Education and Prevention Program. www.nhlbi.nih.gov/guidelines/asthma/ asthgdln.htm. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma 2007. 2007.
27. Bousquet J, Mantzouranis E, Cruz AA, Aït-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. The Journal of allergy and clinical immunology. 2010;126(5):926-38.
28. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. The Journal of allergy and clinical immunology. 2010;126(5):926-38.
29. Abraham B, Antó JM, Barreiro E, Bel EHD, Bonsignore G, Bousquet J, et al. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Respiratory Journal. 2003;22(3):470-7.
30. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. American journal of respiratory and critical care medicine. 2000;162(6):2341-51.
31. Dolan CM, Fraher KE, Bleecker ER, Borish L, Chipps B, Hayden ML, et al. Design and baseline characteristics of The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study: A large cohort of patients with severe or difficult-to-treat asthma. Annals of Allergy, Asthma and Immunology. 2004;92(1):32-9.
32. Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, et al. Diagnosis and definition of severe refractory asthma: An international consensus statement from the innovative medicine initiative (IMI). Thorax. 2011;66(10):910-7.

33. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. The European respiratory journal. 2014;43(2):343-73.
34. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. The Cochrane database of systematic reviews. 2014(11):Cd000011.
35. British Guideline on the Management of Asthma. Thorax. 2008;63 Suppl 4:iv1-121.
36. Guarnaccia S, Lombardi A, Gaffurini A, Chiarini M, Domenighini S, D'Agata E, et al. Application and implementation of the GINA asthma guidelines by specialist and primary care physicians: a longitudinal follow-up study on 264 children. Prim Care Respir J. 2007;16(6):357-62.
37. Osterberg L, Blaschke T. Adherence to medication. The New England journal of medicine. 2005;353(5):487-97.
38. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. The European respiratory journal. 2003;22(3):478-83.
39. Bracken M, Fleming L, Hall P, Van Stiphout N, Bossley C, Biggart E, et al. The importance of nurse-led home visits in the assessment of children with problematic asthma. Arch Dis Child. 2009;94(10):780-4.
40. Desager K, Vermeulen F, Bodart E. Adherence to asthma treatment in childhood and adolescence - a narrative literature review. Acta Clin Belg. 2018;73(5):348-55.
41. Burgess SW, Sly PD, Morawska A, Devadason SG. Assessing adherence and factors associated with adherence in young children with asthma. Respirology (Carlton, Vic). 2008;13(4):559-63.
42. Krishnan JA, Bender BG, Wamboldt FS, Szefler SJ, Adkinson NF, Jr., Zeiger RS, et al. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. The Journal of allergy and clinical immunology. 2012;129(1):112-8.
43. Reznik M, Ozuah PO. Measurement of inhaled corticosteroid adherence in inner-city, minority children with persistent asthma by parental report and integrated dose counter. Journal of allergy. 2012;2012:570850.
44. Armstrong ML, Duncan CL, Stokes JO, Pereira D. Association of caregiver health beliefs and parenting stress with medication adherence in preschoolers with asthma. The Journal of asthma : official journal of the Association for the Care of Asthma. 2014;51(4):366-72.
45. Cerveri I, Locatelli F, Zoia MC, Corsico A, Accordini S, de Marco R. International variations in asthma treatment compliance: the results of the European Community Respiratory Health Survey (ECRHS). The European respiratory journal. 1999;14(2):288-94.
46. Ismaila A, Corriveau D, Vaillancourt J, Parsons D, Stanford R, Su Z, et al. Impact of adherence to treatment with fluticasone propionate/salmeterol in asthma patients. Curr Med Res Opin. 2014;30(7):1417-25.
47. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. The Journal of allergy and clinical immunology. 2011;128(6):1185-91 e2.
48. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respiratory medicine. 2011;105(6):930-8.
49. O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. Thorax. 2015;70(4):376-8.

50. Roland NJ, Bhalla RK, Earis J. The local side effects of inhaled corticosteroids: current understanding and review of the literature. Chest. 2004;126(1):213-9.
51. Kelly HW, Nelson HS. Potential adverse effects of the inhaled corticosteroids. The Journal of allergy and clinical immunology. 2003;112(3):469-78; quiz 79.
52. Wong J, Black P. Acute adrenal insufficiency associated with high dose inhaled steroids. BMJ (Clinical research ed). 1992;304(6839):1415.
53. Albert SG, Slavin RG. Adrenal insufficiency in an adult on inhaled corticosteroids; recovery of adrenal function with inhaled nedocromil sodium. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 1998;81(6):582-4.
54. Lapi F, Kezouh A, Suissa S, Ernst P. The use of inhaled corticosteroids and the risk of adrenal insufficiency. The European respiratory journal. 2013;42(1):79-86.
55. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. American journal of respiratory and critical care medicine. 2009;180(9):817-22.
56. Sanchis J, Corrigan C, Levy ML, Viejo JL. Inhaler devices - from theory to practice. Respiratory medicine. 2013;107(4):495-502.
57. Dolovich M, Ruffin RE, Roberts R, Newhouse MT. Optimal delivery of aerosols from metered dose inhalers. Chest. 1981;80(6 Suppl):911-5.
58. Newman SP, Moren F, Pavia D, Little F, Clarke SW. Deposition of pressurized suspension aerosols inhaled through extension devices. The American review of respiratory disease. 1981;124(3):317-20.
59. Lawford P, McKenzie D. Pressurized aerosol inhaler technique: how important are inhalation from residual volume, inspiratory flow rate and the time interval between puffs? British journal of diseases of the chest. 1983;77(3):276-81.
60. Newman SP, Pavia D, Moren F, Sheahan NF, Clarke SW. Deposition of pressurised aerosols in the human respiratory tract. Thorax. 1981;36(1):52-5.
61. Yokoyama H, Yamamura Y, Ozeki T, Iga T, Yamada Y. Analysis of relationship between peak inspiratory flow rate and amount of drug delivered to lungs following inhalation of fluticasone propionate with a Diskhaler. Biological & pharmaceutical bulletin. 2007;30(1):162-4.
62. Maggi L, Bruni R, Conte U. Influence of the moisture on the performance of a new dry powder inhaler. International journal of pharmaceutics. 1999;177(1):83-91.
63. Jerant A, DiMatteo R, Arnsten J, Moore-Hill M, Franks P. Self-report adherence measures in chronic illness: retest reliability and predictive validity. Medical care. 2008;46(11):1134-9.
64. Sayner R, Carpenter DM, Robin AL, Blalock SJ, Muir KW, Vitko M, et al. How glaucoma patient characteristics, self-efficacy and patient-provider communication are associated with eye drop technique. Int J Pharm Pract. 2016;24(2):78-85.
65. Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: a summary of the literature. Medical care. 2004;42(7):649-52.
66. Bollen JC, Dean SG, Siegert RJ, Howe TE, Goodwin VA. A systematic review of measures of self-reported adherence to unsupervised home-based rehabilitation exercise programmes, and their psychometric properties. BMJ open. 2014;4(6):e005044.
67. Marletta MA. Nitric oxide synthase: aspects concerning structure and catalysis. Cell. 1994;78(6):927-30.
68. Di Rosa M, Radomski M, Carnuccio R, Moncada S. Glucocorticoids inhibit the induction of nitric oxide synthase in macrophages. Biochemical and biophysical research communications. 1990;172(3):1246-52.

69. Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne EA, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. Lancet (London, England). 1994;343(8890):133-5.
70. Kharitonov SA, Yates DH, Barnes PJ. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. American journal of respiratory and critical care medicine. 1996;153(1):454-7.
71. Jatakanon A, Lim S, Kharitonov SA, Chung KF, Barnes PJ. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. Thorax. 1998;53(2):91-5.
72. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. American journal of respiratory and critical care medicine. 2011;184(5):602-15.
73. McNicholl DM, Stevenson M, McGarvey LP, Heaney LG. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. American journal of respiratory and critical care medicine. 2012;186(11):1102-8.
74. Simmons MS, Nides MA, Kleerup EC, Chapman KR, Milgrom H, Rand CS, et al. Validation of the Doser, a new device for monitoring metered-dose inhaler use. The Journal of allergy and clinical immunology. 1998;102(3):409-13.
75. Foster JM, Smith L, Usherwood T, Sawyer SM, Rand CS, Reddel HK. The reliability and patient acceptability of the SmartTrack device: a new electronic monitor and reminder device for metered dose inhalers. The Journal of asthma : official journal of the Association for the Care of Asthma. 2012;49(6):657-62.
76. Julius SM, Sherman JM, Hendeles L. Accuracy of three electronic monitors for metered-dose inhalers. Chest. 2002;121(3):871-6.
77. Patel M, Pilcher J, Travers J, Perrin K, Shaw D, Black P, et al. Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. The journal of allergy and clinical immunology In practice. 2013;1(1):83-91.
78. Merchant RK, Inamdar R, Quade RC. Effectiveness of Population Health Management Using the Propeller Health Asthma Platform: A Randomized Clinical Trial. The journal of allergy and clinical immunology In practice. 2016;4(3):455-63.
79. Burgess SW, Wilson SS, Cooper DM, Sly PD, Devadason SG. In vitro evaluation of an asthma dosing device: the smart-inhaler. Respiratory medicine. 2006;100(5):841-5.
80. Chan AH, Reddel HK, Apter A, Eakin M, Riekert K, Foster JM. Adherence monitoring and e-health: how clinicians and researchers can use technology to promote inhaler adherence for asthma. The journal of allergy and clinical immunology In practice. 2013;1(5):446-54.
81. Chan AHY, Reddel HK, Apter A, Eakin M, Riekert K, Foster JM. Adherence Monitoring and E-Health: How Clinicians and Researchers Can Use Technology to Promote Inhaler Adherence for Asthma. Journal of Allergy and Clinical Immunology: In Practice. 2013;1(5):446-54.
82. Sulaiman I, Greene G, MacHale E, Seheult J, Mokoka M, D'Arcy S, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. The European respiratory journal. 2018;51(1).
83. O'Dwyer SM, MacHale E, Sulaiman I, Holmes M, Hughes C, D'Arcy S, et al. The effect of providing feedback on inhaler technique and adherence from an electronic audio recording device, INCA(R), in a community pharmacy setting: study protocol for a randomised controlled trial. Trials. 2016;17(1):226.
84. Yach D. World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. Geneva, World Health Organization, 2003. Available from: http://apps.who.int/medicinedocs/pdf/s4883e/s4883e.pdf. 2003.

85. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol. 1986;136(7):2348-57.
86. Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. The Journal of clinical investigation. 2008;118(11):3546-56.
87. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: The next steps toward personalized care. Journal of Allergy and Clinical Immunology. 2015;135(2):299-311.
88. Milgrom H, Fick RB, Jr., Su JQ, Reimann JD, Bush RK, Watrous ML, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. The New England journal of medicine. 1999;341(26):1966-73.
89. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy: European Journal of Allergy and Clinical Immunology. 2005;60(3):309-16.
90. Buhl R, Hanf G, Soler M, Bensch G, Wolfe J, Everhard F, et al. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. European Respiratory Journal. 2002;20(5):1088-94.
91. Flood-Page P, Menzies-Gow A, Phipps S, Ying S, Wangoo A, Ludwig MS, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. The Journal of clinical investigation. 2003;112(7):1029-36.
92. Menzies-Gow A, Flood-Page P, Sehmi R, Burman J, Hamid Q, Robinson DS, et al. Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics. The Journal of allergy and clinical immunology. 2003;111(4):714-9.
93. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet (London, England). 2000;356(9248):2144-8.
94. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. The New England journal of medicine. 2017;376(25):2448-58.
95. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. New England Journal of Medicine. 2014;371(13):1189-97.
96. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. New England Journal of Medicine. 2014;371(13):1198-207 10p.
97. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. New England Journal of Medicine. 2009;360(10):973-84.
98. Egan RW, Athwal D, Bodmer MW, Carter JM, Chapman RW, Chou CC, et al. Effect of Sch 55700, a humanized monoclonal antibody to human interleukin-5, on eosinophilic responses and bronchial hyperreactivity. Arzneimittel-Forschung. 1999;49(9):779-90.
99. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. Chest. 2016;150(4):799-810.
100. Castro M, Mathur S, Hargreave F, Xie F, Young J, Wilkins HJ, et al. Reslizumab in the treatment of poorly controlled asthma in patients with eosinophilic airway inflammation. Annals of Allergy, Asthma and Immunology Conference: 2010 Annual Meeting of the

American College of Allergy, Asthma and Immunology Phoenix, Arizona United States Conference Start: 20101111 Conference End: 20101116 Conference Publication: (varpagings) [Internet]. 2010; 105(5):[A43 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/584/CN-00833584/frame.html.
101. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. New England Journal of Medicine. 2013;368(26):2455-66.
102. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. The New England journal of medicine. 2018;378(26):2486-96.
103. Hanania NA, Korenblat P, Chapman KR, Bateman ED, Kopecky P, Paggiaro P, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. Lancet Respir Med. 2016;4(10):781-96.
104. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic cor ticosteroid unresponsive asthma. The Lancet. 1999;353(9171):2213-4.
105. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. American journal of respiratory and critical care medicine. 2009;180(5):388-95.
106. Baines KJ, Simpson JL, Wood LG, Scott RJ, Gibson PG. Transcriptional phenotypes of asthma defined by gene expression profiling of induced sputum samples. The Journal of allergy and clinical immunology. 2011;127(1):153-60, 60.e1-9.
107. McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. American journal of respiratory and critical care medicine. 2012;185(6):612-9.
108. Chapman RW, Minnicozzi M, Celly CS, Phillips JE, Kung TT, Hipkin RW, et al. A novel, orally active CXCR1/2 receptor antagonist, Sch527123, inhibits neutrophil recruitment, mucus production, and goblet cell hyperplasia in animal models of pulmonary inflammation. The Journal of pharmacology and experimental therapeutics. 2007;322(2):486-93.
109. Nair P, Gaga M, Zervas E, Alagha K, Hargreave FE, O'Byrne PM, et al. Safety and efficacy of a CXCR2 antagonist in patients with severe asthma and sputum neutrophils: a randomized, placebo-controlled clinical trial. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2012;42(7):1097-103.
110. Nair P, Gaga M, Zervas E, Alagha K, Hargreave FE, O'Byrne PM, et al. Safety and efficacy of a CXCR2 antagonist in patients with severe asthma and sputum neutrophils: a randomized, placebo-controlled clinical trial. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology [Internet]. 2012; 42(7):[1097-103 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/445/CN-00834445/frame.html.
111. Global Initiative for Asthma (GINA).Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention LuAfwgo, Accessed April 27. <GINA_Report_2015_Aug11.pdf>.
112. Apter AJ, Boston RC, George M, Norfleet AL, Tenhave T, Coyne JC, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. The Journal of allergy and clinical immunology. 2003;111(6):1219-26.
113. Wilson SR, Strub P, Buist AS, Knowles SB, Lavori PW, Lapidus J, et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. American journal of respiratory and critical care medicine. 2010;181(6):566-77.
114. George M, Freedman TG, Norfleet AL, Feldman HI, Apter AJ. Qualitative research-enhanced understanding of patients' beliefs: results of focus groups with low-income, urban,

African American adults with asthma. The Journal of allergy and clinical immunology. 2003;111(5):967-73.
115. Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, et al. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet (London, England). 2017;389(10065):157-66.
116. Peters SP, Bleecker ER, Canonica GW, Park YB, Ramirez R, Hollis S, et al. Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone. The New England journal of medicine. 2016;375(9):850-60.
117. Bateman E, Hurd S, Barnes P, Bousquet J, Drazen J, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. European Respiratory Journal. 2008;31(1):143-78.
118. Robinson DS, Kariyawasam HH, Heaney LG. Phase three studies of biologics for severe asthma: could do better? The European respiratory journal. 2017;50(3).
119. Dutile S, Kaptchuk TJ, Wechsler ME. The placebo effect in asthma. Curr Allergy Asthma Rep. 2014;14(8):456.
120. Wechsler ME, Kelley JM, Boyd IO, Dutile S, Marigowda G, Kirsch I, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. The New England journal of medicine. 2011;365(2):119-26.
121. Adair JG. The Hawthorne effect: A reconsideration of the methodological artifact. Journal of Applied Psychology. 1984;69(2):334-45.
122. Shiovitz TM, Bain EE, McCann DJ, Skolnick P, Laughren T, Hanina A, et al. Mitigating the Effects of Nonadherence in Clinical Trials. J Clin Pharmacol. 2015.
123. RevMan R. The nordic cochrane centre, the cochrane collaboration. Book [computer program]. version; 2014.
124. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327(7414):557-60.
125. Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration, 2011. Available from: Available from http://handbook.cochrane.org.
126. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed). 2009;339:b2535.
127. Shapiro G, Lumry W, Wolfe J, Given J, White MV, Woodring A, et al. Combined salmeterol 50 microg and fluticasone propionate 250 microg in the diskus device for the treatment of asthma. American journal of respiratory and critical care medicine. 2000;161(2 Pt 1):527-34.
128. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for Inadequately Controlled Asthma with Elevated Blood Eosinophil Levels: a Randomized Phase 3 Study. Chest. 2016.
129. Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Allergy: European Journal of Allergy and Clinical Immunology. 2004;59(7):701-8.
130. Bardelas J, Figliomeni M, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. Journal of Asthma. 2012;49(2):144-52.
131. Beeh KM, Moroni-Zentgraf P, Ablinger O, Hollaenderova Z, Unseld A, Engel M, et al. Tiotropium Respimat (R) in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma. Respiratory Research. 2014;15.

132. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, et al. Evidence of a role of tumor necrosis factor α in refractory asthma. New England Journal of Medicine. 2006;354(7):697-708.
133. Bjermer L, Lemiere C, Maspero J, Ciesielska M, O'Brien C, Zangrilli J. A randomized phase 3 study of the efficacy and safety of reslizumab in subjects with asthma with elevated eosinophils. European Respiratory Journal. 2014;44.
134. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet (London, England). 2016;388(10056):2115-27.
135. Brightling CE, Chanez P, Leigh R, O'Byrne PM, Korn S, She D. Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: A randomised, double-blind, placebo-controlled, phase 2b trial. Lancet Respiratory Medicine [Internet]. 2015; 3(9):[692-701 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/062/CN-01092062/frame.html.
136. Brinke A, Goos C, Timmers M, vd Veen H, Sterk P, Rabe K, et al. Persistent sputum eosinophilia in severe asthma despite treatment: The triamcinolone experience [abstract]. American journal of respiratory and critical care medicine [Internet]. 2001; 163(5 Suppl):[A871 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/316/CN-00592316/frame.html.
137. Brusselle GG, Vanderstichele C, Jordens P, Deman R, Slabbynck H, Ringoet V, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax [Internet]. 2013; 68(4):[322-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/004/CN-00849004/frame.html.
138. Busse WW. Anti-immunoglobulin E (omalizumab) therapy in allergic asthma. American journal of respiratory and critical care medicine. 2001;164(8 Pt 2):S12-S7.
139. Busse WW, Holgate S, Kerwin E, Chon Y, Feng J, Lin J, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. American journal of respiratory and critical care medicine. 2013;188(11):1294-302.
140. Busse WW, Israel E, Nelson HS, Baker JW, Charous BL, Young DY, et al. Daclizumab improves asthma control in patients with moderate to severe persistent asthma: a randomized, controlled trial. American journal of respiratory and critical care medicine. 2008;178(10):1002-8.
141. Busse WW, Wenzel SE, Meltzer EO, Kerwin EM, Liu MC, Zhang N, et al. Safety and efficacy of the prostaglandin D2 receptor antagonist AMG 853 in asthmatic patients. Journal of Allergy and Clinical Immunology. 2013;131(2):339-45.
142. Cahill KN, Katz HR, Cui J, Lai J, Kazani S, Crosby-Thompson A, et al. KIT Inhibition by Imatinib in Patients with Severe Refractory Asthma. The New England journal of medicine. 2017;376(20):1911-20.
143. Castro M, Rubin AS, Laviolette M, Fiterman J, Andrade Lima M, Shah PL, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. American journal of respiratory and critical care medicine [Internet]. 2010; 181(2):[116-24 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/207/CN-00730207/frame.html.

144. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respiratory Medicine [Internet]. 2014. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/379/CN-01017379/frame.html.
145. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle G, Bardin PG. Reslizumab treatment for moderate to severe asthma with elevated blood eosinophil levels. Journal of Allergy and Clinical Immunology [Internet]. 2015; 135(2 Suppl 1):[Ab381 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/040/CN-01051040/frame.html.
146. Chanez P, Contin-Bordes C, Garcia G, Verkindre C, Didier A, Blay F, et al. Omalizumab-induced decrease of Fc?RI expression in patients with severe allergic asthma. Respiratory medicine [Internet]. 2010; 104(11):[1608-17 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/125/CN-00769125/frame.html.
147. Corren J, Busse W, Meltzer EO, Mansfield L, Bensch G, Fahrenholz J, et al. A randomized, controlled, phase 2 study of AMG 317, an IL-4Ralpha antagonist, in patients with asthma. American journal of respiratory and critical care medicine. 2010;181(8):788-96.
148. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. The New England journal of medicine. 2011;365(12):1088-98.
149. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al. Asthma control during the year after bronchial thermoplasty. New England Journal of Medicine. 2007;356(13):1327-37.
150. Coyle TB, Metersky ML. The effect of the endothelin-1 receptor antagonist, bosentan, on patients with poorly controlled asthma: A 17-week, double-blind, placebo-controlled crossover pilot study. Journal of Asthma. 2013;50(4):433-7.
151. De Boever EH, Ashman C, Cahn AP, Locantore NW, Overend P, Pouliquen IJ, et al. Efficacy and safety of an anti-IL-13 mAb in patients with severe asthma: a randomized trial. The Journal of allergy and clinical immunology. 2014;133(4):989-96.
152. Dente FL, Bacci E, Bartoli ML, Cianchetti S, Costa F, Di Franco A, et al. Effects of oral prednisone on sputum eosinophils and cytokines in patients with severe refractory asthma. Annals of Allergy, Asthma and Immunology. 2010;104(6):464-70.
153. Erin EM, Leaker BR, Nicholson GC, Tan AJ, Green LM, Neighbour H, et al. The effects of a monoclonal antibody directed against tumor necrosis factor-alpha in asthma. American journal of respiratory and critical care medicine [Internet]. 2006; 174(7):[753-62 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/531/CN-00566531/frame.html.
154. Fernandes ALG, Amorim MM, Caetano LB, Dracoulakis S, Araruna AAR, Faresin SM, et al. Bronchodilator response as a hallmark of uncontrolled asthma: a randomised clinical trial. The Journal Of Asthma: Official Journal Of The Association For The Care Of Asthma. 2014;51(4):405-10.
155. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet (London, England). 2016;388(10056):2128-41.
156. Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. American journal of respiratory and critical care medicine. 2007;176(11):1062-71.

157. Gao JM, Cai F, Peng M, Ma Y, Wang B. Montelukast improves air trapping, not airway remodeling, in patients with moderate-to-severe asthma: A pilot study. Chinese Medical Journal. 2013;126(12):2229-34.
158. Garcia G, Magnan A, Chiron R, Contin-Bordes C, Berger P, Taillé C, et al. A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma. Chest [Internet]. 2013; 144(2):[411-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/766/CN-00872766/frame.html.
159. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol. 2013;131(1):110-6.e1.
160. Girodet PO, Dournes G, Thumerel M, Begueret H, Dos Santos P, Ozier A. A double-blind, placebo-controlled trial of gallopamil for severe asthma. American journal of respiratory and critical care medicine [Internet]. 2015; 191(Meeting Abstracts):[A5148 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/078/CN-01101078/frame.html.
161. Gotfried MH, Jung R, Messick CR, Rubinstein I, Garey KW, Rodvold KA, et al. Effects of six-week clarithromycin therapy in corticosteroid-dependent asthma: A randomized, double-blind, placebo-controlled pilot study. Current Therapeutic Research - Clinical and Experimental. 2004;65(1):1-12.
162. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: A randomized trial. Annals of Internal Medicine. 2011;154(9):573-82.
163. Hanania NA, Noonan M, Corren J, Korenblat P, Zheng Y, Fischer SK. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. Thorax [Internet]. 2015. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/983/CN-01072983/frame.html.
164. Hedman J, Seideman P, Albertioni F, Stenius-Aarniala B. Controlled trial of methotrexate in patients with severe chronic asthma. European Journal of Clinical Pharmacology. 1996;49(5):347-9.
165. Hodgson D, Anderson J, Reynolds C, Meakin G, Bailey H, Pavord I, et al. A randomised controlled trial of small particle inhaled steroids in refractory eosinophilic asthma (SPIRA). Thorax. 2015;70(6):559-65.
166. Holgate ST, Chuchalin AG, Hébert J, Lötvall J, Persson GB, Chung KF, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clinical and experimental allergy [Internet]. 2004; 34(4):[632-8 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/728/CN-00467728/frame.html.
167. Holgate ST, Noonan M, Chanez P, Busse W, Dupont L, Pavord I, et al. Efficacy and safety of etanercept in moderate-to-severe asthma: A randomised, controlled trial. European Respiratory Journal. 2011;37(6):1352-9.
168. Humbert M, Blay F, Garcia G, Prud'homme A, Leroyer C, Magnan A, et al. Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics. Allergy [Internet]. 2009; 64(8):[1194-201 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/754/CN-00719754/frame.html.
169. Juergens UR, Dethlefsen U, Steinkamp G, Gillissen A, Repges R, Vetter H. Anti-inflammatory activity of 1.8-cineol (eucalyptol) in bronchial asthma: A double-blind placebo-controlled trial. Respiratory medicine. 2003;97(3):250-6.

170. Kaler M, Barochia AV, Weir NA, Cuento RA, Stylianou M, Roth MJ, et al. A randomized, placebo-controlled, double-blinded, crossover trial of pioglitazone for severe asthma. J Allergy Clin Immunol. 2017;140(6):1716-8.
171. Kanzow G, Nowak D, Magnussen H. SHORT-TERM EFFECT OF METHOTREXATE IN SEVERE STEROID-DEPENDENT ASTHMA. Lung. 1995;173(4):223-31.
172. Kenyon NJ, Last M, Bratt JM, Kwan VW, O'Roark E, Linderholm A. L-arginine supplementation and metabolism in asthma. Pharmaceuticals. 2011;4(1):187-201.
173. Kerstjens HA, Disse B, Schröder-Babo W, Bantje TA, Gahlemann M, Sigmund R, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. Journal of allergy and clinical immunology [Internet]. 2011; 128(2):[308-14 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/581/CN-00799581/frame.html.
174. Kishiyama JL, Valacer D, Cunningham-Rundles C, Sperber K, Richmond GW, Abramson S, et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. Clinical Immunology. 1999;91(2):126-33.
175. Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. Omalizumab is effective in the long-term control of severe allergic asthma. Annals of Allergy, Asthma & Immunology. 2003;91(2):154-9 6p.
176. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol. 2013;132(5):1086-96.e5.
177. Li J, Kang J, Canvin J, Wang C, Zhong N, Yang J. Omalizumab improves quality of life and asthma control in chinese patients with moderate-to-severe asthma: A randomized phase III study. Respirology (Carlton, Vic) [Internet]. 2014; 19(Suppl 3):[2 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/042/CN-01020042/frame.html.
178. Lock SH, Kay AB, Barnes NC. Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing agent in corticosteroid-dependent asthma. American journal of respiratory and critical care medicine. 1996;153(2):509-14.
179. Lomia M, Tchelidze T, Pruidze M. Bronchial asthma as neurogenic paroxysmal inflammatory disease: A randomized trial with carbamazepine. Respiratory medicine. 2006;100(11):1988-96.
180. Marin JM, Carrizo SJ, Garcia R, Ejea MV. Effects of nedocromil sodium in steroid-resistant asthma: A randomized controlled trial. Journal of Allergy and Clinical Immunology. 1996;97(2):602-10.
181. Morjaria JB, Chauhan AJ, Babu KS, Polosa R, Davies DE, Holgate ST. The role of a soluble TNFα receptor fusion protein (etanercept) in corticosteroid refractory asthma: A double blind, randomised, placebo controlled trial. Thorax. 2008;63(7):584-91.
182. Nair P, Gaga M, Zervas E, Alagha K, Hargreave FE, O'Byrne PM, et al. Safety and efficacy of a CXCR2 antagonist in patients with severe asthma and sputum neutrophils: a randomized, placebo-controlled clinical trial. Clinical And Experimental Allergy: Journal Of The British Society For Allergy And Clinical Immunology. 2012;42(7):1097-103.
183. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009;360(10):985-93.
184. Nizankowska E, Soja J, Pinis G, Bochenek G, K Sa, Domaga?a B, et al. Treatment of steroid-dependent bronchial asthma with cyclosporin. The European respiratory journal [Internet]. 1995; 8(7):[1091-9 pp.]. Available from:

http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/809/CN-00118809/frame.html.
185. Ogirala RG, Sturm TM, Aldrich TK, Meller FF, Pacia EB, Keane AM, et al. Single, high-dose intramuscular triamcinolone acetonide versus weekly oral methotrexate in life-threatening asthma: A double-blind study. American journal of respiratory and critical care medicine. 1995;152(5 I):1461-6.
186. Oh CK, Leigh R, McLaurin KK, Kim K, Hultquist M, Molfino NA. A randomized, controlled trial to evaluate the effect of an anti-interleukin-9 monoclonal antibody in adults with uncontrolled asthma. Respiratory Research. 2013;14(1).
187. Ohta K, Miyamoto T, Amagasaki T, Yamamoto M. Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma. Respirology (Carlton, Vic). 2009;14(8):1156-65.
188. Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K, et al. A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan. Int Arch Allergy Immunol. 2016;169(3):135-45.
189. Pavord I, Korn S, Howarth P, Bleecker E, Buhl R, Keene O, et al. Mepolizumab (anti-IL-5) reduces exacerbations in patients with refractory eosinophilic asthma. European respiratory journal [Internet]. 2012; 40. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/433/CN-01100433/frame.html.
190. Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. Lancet (London, England) [Internet]. 2001; 357(9273):[2007-11 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/243/CN-00349243/frame.html.
191. Rubin AS, Souza-Machado A, Andradre-Lima M, Ferreira F, Honda A, Matozo TM. Effect of omalizumab as add-on therapy on asthma-related quality of life in severe allergic asthma: a Brazilian study (QUALITX). J Asthma. 2012;49(3):288-93.
192. Salmun LM, Barlan I, Wolf HM, Eibl M, Twarog FJ, Geha RS, et al. Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: A double-blind, placebo-controlled, randomized trial. Journal of Allergy and Clinical Immunology. 1999;103(5 I):810-5.
193. Sano Y, Adachi M, Kiuchi T, Miyamoto T. Effects of nebulized sodium cromoglycate on adult patients with severe refractory asthma. Respiratory medicine. 2006;100(3):420-33.
194. Bousquet J, Siergiejko Z, Swiebocka E, Humbert M, Rabe KF, Smith N, et al. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. Allergy. 2011;66(5):671-8.
195. Simpson JL, Powell H, Boyle MJ, Scott RJ, Gibson PG. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. American journal of respiratory and critical care medicine. 2008;177(2):148-55.
196. Smith LJ, Kalhan R, Wise RA, Sugar EA, Lima JJ, Irvin CG, et al. Effect of a Soy Isoflavone Supplement on Lung Function and Clinical Outcomes in Patients With Poorly Controlled Asthma A Randomized Clinical Trial. Jama-Journal of the American Medical Association. 2015;313(20):2033-43.
197. Soler M. Omalizumab, a monoclonal antibody against IgE for the treatment of allergic diseases. International Journal of Clinical Practice. 2001;55(7):480-3.
198. Tamaoki J, Kondo M, Sakai N, Aoshiba K, Tagaya E, Nakata J, et al. Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid-dependent asthma: A double-blind randomised study. Lancet (London, England). 2000;356(9226):273-8.
199. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with

concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy. 2004;59(7):709-17.
200. Virchow JC, Prasse A, Naya I, Summerton L, Harris A. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. American journal of respiratory and critical care medicine [Internet]. 2000; 162(2 Pt 1):[578-85 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/916/CN-00298916/frame.html.
201. Wang N, Li J, Huang X, Chen W, Chen Y. Herbal Medicine Cordyceps sinensis Improves Health-Related Quality of Life in Moderate-to-Severe Asthma. Evidence-based complementary and alternative medicine : eCAM. 2016;2016:6134593.
202. Wenzel SE, Robinson CB, Leonard JM, Panettieri Jr RA. Nebulized dehydroepiandrosterone-3-sulfate improves asthma control in the moderate-to-severe asthma results of a 6-week, randomized, double-blind, placebo-controlled study. Allergy and asthma proceedings. 2010;31(6):461-71.
203. Wenzel SE, Barnes PJ, Bleecker ER, Bousquet J, Busse W, Dahlén SE, et al. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-α blockade in severe persistent asthma. American journal of respiratory and critical care medicine. 2009;179(7):549-58.
204. Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. American Journal of Respiratory & Critical Care Medicine. 2007;176(12):1185-91 7p.
205. Corren J, Weinstein S, Janka L, O'Brien C, Zangrilli J. A randomized phase 3 study of reslizumab efficacy in relation to blood eosinophil levels in patients with moderate to severe asthma. European Respiratory Journal. 2014;44.
206. Brusselle GG, Vander Stichele C, Jordens P, Deman R, Slabbynck H, Ringoet V, et al. The azithromycin in severe asthma (AZISAST) study: Accurate classification into the five severe asthma research program (SARP) clinical phenotypes of severe asthma. American journal of respiratory and critical care medicine [Internet]. 2012; 185. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/739/CN-01091739/frame.html.
207. Humbert M, De Blay F, Garcia G, Prud'Homme A, Leroyer C, Magnan A, et al. Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics. Allergy: European Journal of Allergy and Clinical Immunology. 2009;64(8):1194-201.
208. Castro M, Musani AI, Mayse ML, Shargill NS. Bronchial thermoplasty: a novel technique in the treatment of severe asthma. Therapeutic Advances In Respiratory Disease. 2010;4(2):101-16.
209. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: Results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. The Lancet Respiratory Medicine. 2015;3(5):355-66.
210. Kerstjens H, Dahl R, Beck E, Vandewalker M, Engel M, Sigmund R. Tiotropium reduces asthma exacerbations in patients with uncontrolled asthma and persistent airflow obstruction despite treatment in accordance with guidelines. Respirology (Carlton, Vic) [Internet]. 2012; 17:[16 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/738/CN-00985738/frame.html.
211. Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M. Tiotropium respimat add-on therapy to inhaled corticosteroids (ICS) + long-acting beta2-agonists (LABAS) in patients with symptomatic severe asthma: Efficacy by level of airway obstruction. American journal of respiratory and critical care medicine [Internet]. 2014; 189. Available

from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/012/CN-01107012/frame.html.
212. McCann DJ, Petry NM, Bresell A, Isacsson E, Wilson E, Alexander RC. Medication Nonadherence, "Professional Subjects," and Apparent Placebo Responders: Overlapping Challenges for Medications Development. J Clin Psychopharmacol. 2015;35(5):566-73.
213. Busse WW, Lemanske RF, Jr. The placebo effect in asthma: Far more complex than simply "I shall please". J Allergy Clin Immunol. 2009;124(3):445-6.
214. Heaney LG, Horne R. Non-adherence in difficult asthma: time to take it seriously. Thorax. 2012;67(3):268-70.
215. Ortega H, Chupp G, Bardin P, Bourdin A, Garcia G, Hartley B, et al. The role of mepolizumab in atopic and nonatopic severe asthma with persistent eosinophilia. The European respiratory journal. 2014;44(1):239-41.
216. Wenzel SE, Wang L, Pirozzi G, Sutherland ER, Graham N, Evans R, et al. Dupilumab improves lung function and reduces severe exacerbations in uncontrolled asthmatics with baseline eosinophil levels above and below 300 cells/µl. American journal of respiratory and critical care medicine. 2015;191.
217. Braunstein GL, Trinquet G, Harper AE. Compliance with nedocromil sodium and a nedocromil sodium/salbutamol combination. Compliance Working Group. The European respiratory journal. 1996;9(5):893-8.
218. Bosley CM, Fosbury JA, Cochrane GM. The psychological factors associated with poor compliance with treatment in asthma. The European respiratory journal. 1995;8(6):899-904.
219. Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. The European respiratory journal. 1999;13(5):1198-208.
220. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther. 1999;21(6):1074-90; discussion 3.
221. Sulaiman I, Cushen B, Greene G, Seheult J, Seow D, Rawat F, et al. Objective Assessment of Adherence to Inhalers by COPD Patients. American journal of respiratory and critical care medicine. 2016.
222. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. The European respiratory journal. 2014;43(2):343-73.
223. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. A new perspective on concepts of asthma severity and control. The European respiratory journal. 2008;32(3):545-54.
224. Bel E, Ten Brinke A. A rational approach to the management of severe refractory asthma. Treatments in respiratory medicine. 2005;4(6):365-79.
225. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet . 2002;360(9347):1715-21.
226. van Veen IH, Ten Brinke A, Gauw SA, Sterk PJ, Rabe KF, Bel EH. Consistency of sputum eosinophilia in difficult-to-treat asthma: a 5-year follow-up study. The Journal of allergy and clinical immunology. 2009;124(3):615-7, 7.e1-2.
227. ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. Factors associated with persistent airflow limitation in severe asthma. American journal of respiratory and critical care medicine. 2001;164(5):744-8.
228. Strunk RC, Bloomberg GR. Omalizumab for asthma. The New England journal of medicine. 2006;354(25):2689-95.

229. Jatakanon A, Uasuf C, Maziak W, Lim S, Chung KF, Barnes PJ. Neutrophilic inflammation in severe persistent asthma. American journal of respiratory and critical care medicine. 1999;160(5 Pt 1):1532-9.
230. Wenzel SE, Szefler SJ, Leung DY, Sloan SI, Rex MD, Martin RJ. Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. American journal of respiratory and critical care medicine. 1997;156(3 Pt 1):737-43.
231. Taylor TE, Zigel Y, De Looze C, Sulaiman I, Costello RW, Reilly RB. Advances in Audio-Based Systems to Monitor Patient Adherence and Inhaler Drug Delivery. Chest. 2017.
232. McCartan TA, Taylor TE, Sulaiman I, Costello RW, Reilly RB. Changes in inhaler inhalation acoustic features during induced bronchoconstriction: a pilot study. Conf Proc IEEE Eng Med Biol Soc. 2016;2016:3749-52.
233. Taylor TE, Holmes MS, Sulaiman I, Costello RW, Reilly RB. Monitoring Inhaler Inhalations Using an Acoustic Sensor Proximal to Inhaler Devices. J Aerosol Med Pulm Drug Deliv. 2016;29(5):439-46.
234. Taylor TE, Holmes MS, Sulaiman I, Costello RW, Reilly RB. Influences of gender and anthropometric features on inspiratory inhaler acoustics and peak inspiratory flow rate. Conf Proc IEEE Eng Med Biol Soc. 2015;2015:2227-30.
235. Taylor TE, Holmes MS, Sulaiman I, D'Arcy S, Costello RW, Reilly RB. An acoustic method to automatically detect pressurized metered dose inhaler actuations. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:4611-4.
236. Holmes MS, Seheult JN, O'Connell P, D'Arcy S, Ehrhardt C, Healy AM, et al. An Acoustic-Based Method to Detect and Quantify the Effect of Exhalation into a Dry Powder Inhaler. Journal of aerosol medicine and pulmonary drug delivery. 2015;28(4):247-53.
237. D'Arcy S, MacHale E, Seheult J, Holmes MS, Hughes C, Sulaiman I, et al. A method to assess adherence in inhaler use through analysis of acoustic recordings of inhaler events. PLoS One. 2014;9(6):e98701.
238. Seheult JN, O'Connell P, Tee KC, Bholah T, Al Bannai H, Sulaiman I, et al. The acoustic features of inhalation can be used to quantify aerosol delivery from a Diskus dry powder inhaler. Pharm Res. 2014;31(10):2735-47.
239. Holmes MS, D'Arcy S, Costello RW, Reilly RB. Acoustic Analysis of Inhaler Sounds From Community-Dwelling Asthmatic Patients for Automatic Assessment of Adherence. IEEE J Transl Eng Health Med. 2014;2:2700210.
240. Holmes MS, Seheult J, Geraghty C, D'Arcy S, Costello RW, Reilly RB. Using acoustics to estimate inspiratory flow rate and drug removed from a dry powder inhaler. Conf Proc IEEE Eng Med Biol Soc. 2013;2013:6866-9.
241. Holmes MS, D'Arcy S, Costello RW, Reilly RB. An acoustic method of automatically evaluating patient inhaler technique. Conf Proc IEEE Eng Med Biol Soc. 2013;2013:1322-5.
242. Holmes MS, Seheult JN, Geraghty C, D'Arcy S, O'Brien U, Crispino O'Connell G, et al. A method of estimating inspiratory flow rate and volume from an inhaler using acoustic measurements. Physiol Meas. 2013;34(8):903-14.
243. Holmes MS, Le Menn M, D'Arcy S, Rapcan V, MacHale E, Costello RW, et al. Automatic identification and accurate temporal detection of inhalations in asthma inhaler recordings. Conf Proc IEEE Eng Med Biol Soc. 2012;2012:2595-8.
244. Moran C, Doyle F, Sulaiman I, Bennett K, Greene G, Molloy GJ, et al. The INCA(TM) (Inhaler Compliance Assessment(TM)): A comparison with established measures of adherence. Psychol Health. 2017;32(10):1266-87.
245. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. Lancet (London, England). 1999;353(9171):2213-4.

246. McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. American journal of respiratory and critical care medicine. 2012;185(6):612-9.
247. Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. American journal of respiratory and critical care medicine. 2003;167(12):1655-9.
248. Niven R, Chung KF, Panahloo Z, Blogg M, Ayre G. Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: An open-label study. Respiratory medicine. 2008;102(10):1371-8.
249. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet (London, England). 2012;380(9842):651-9.
250. Pelaia C, Vatrella A, Busceti MT, Gallelli L, Terracciano R, Savino R, et al. Severe eosinophilic asthma: from the pathogenic role of interleukin-5 to the therapeutic action of mepolizumab. Drug design, development and therapy. 2017;11:3137-44.
251. Mokoka MC, Lombard L, MacHale EM, Walsh J, Cushen B, Sulaiman I, et al. In patients with severe uncontrolled asthma, does knowledge of adherence and inhaler technique using electronic monitoring improve clinical decision making? A protocol for a randomised controlled trial. BMJ Open. 2017;7(6):e015367.
252. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. The European respiratory journal. 2005;26(2):319-38.
253. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. The Journal of allergy and clinical immunology. 2009;124(4):719-23.e1.
254. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax. 1992;47(2):76-83.
255. Whalley D, Globe G, Crawford R, Doward L, Tafesse E, Brazier J, et al. Is the EQ-5D fit for purpose in asthma? Acceptability and content validity from the patient perspective. Health and quality of life outcomes. 2018;16(1):160.
256. Pickard AS, Wilke C, Jung E, Patel S, Stavem K, Lee TA. Use of a preference-based measure of health (EQ-5D) in COPD and asthma. Respiratory medicine. 2008;102(4):519-36.
257. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics. 1993;4(5):353-65.
258. Mac Hale E. INCA training video. 2015 hwic. INCA training video. 2015, http://www. incadevice. com/

patients/ . 2015.
259. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. European Respiratory Journal. 2014;43(2):343-73.
260. Braunstahl GJ, Hellings PW. Allergic rhinitis and asthma: the link further unraveled. Current opinion in pulmonary medicine. 2003;9(1):46-51.
261. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8-160.
262. Price D, Zhang Q, Kocevar VS, Yin DD, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2005;35(3):282-7.

263. Dixon AE, Kaminsky DA, Holbrook JT, Wise RA, Shade DM, Irvin CG. Allergic rhinitis and sinusitis in asthma: differential effects on symptoms and pulmonary function. Chest [Internet]. 2006; 130(2):[429-35 pp.].
264. Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. The Journal of allergy and clinical immunology. 2002;109(1):57-62.
265. ten Brinke A, Grootendorst DC, Schmidt JT, De Bruine FT, van Buchem MA, Sterk PJ, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. The Journal of allergy and clinical immunology. 2002;109(4):621-6.
266. Ceylan E, Gencer M, San I. Nasal polyps and the severity of asthma. Respirology. 2007;12(2):272-6.
267. Lamblin C, Bolard F, Gosset P, Tsicopoulos A, Perez T, Darras J, et al. Bronchial interleukin-5 and eotaxin expression in nasal polyposis. Relationship with (a)symptomatic bronchial hyperresponsiveness. American journal of respiratory and critical care medicine. 2001;163(5):1226-32.
268. Tsicopoulos A, Shimbara A, de Nadai P, Aldewachi O, Lamblin C, Lassalle P, et al. Involvement of IL-9 in the bronchial phenotype of patients with nasal polyposis. The Journal of allergy and clinical immunology. 2004;113(3):462-9.
269. Littner MR, Leung FW, Ballard ED, 2nd, Huang B, Samra NK. Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. Chest. 2005;128(3):1128-35.
270. Coughlan JL, Gibson PG, Henry RL. Medical treatment for reflux oesophagitis does not consistently improve asthma control: a systematic review. Thorax. 2001;56(3):198-204.
271. Lang JE, Holbrook JT, Wise RA, Dixon AE, Teague WG, Wei CY, et al. Obesity in children with poorly controlled asthma: Sex differences. Pediatric pulmonology [Internet]. 2013; 48(9):[847-56 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/285/CN-01000285/frame.html.
272. Beckett WS, Jacobs DR, Jr., Yu X, Iribarren C, Williams OD. Asthma is associated with weight gain in females but not males, independent of physical activity. American journal of respiratory and critical care medicine. 2001;164(11):2045-50.
273. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. Respiratory medicine. 2006;100(4):648-57.
274. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Asthma severity is associated with body mass index and early menarche in women. American journal of respiratory and critical care medicine. 2005;171(4):334-9.
275. Shore SA. Obesity and asthma: possible mechanisms. The Journal of allergy and clinical immunology. 2008;121(5):1087-93; quiz 94-5.
276. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? Chest. 2008;134(2):317-23.
277. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DY. Body mass and glucocorticoid response in asthma. American journal of respiratory and critical care medicine. 2008;178(7):682-7.
278. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. The European respiratory journal. 2006;27(3):495-503.
279. Mosen DM, Schatz M, Magid DJ, Camargo CA, Jr. The relationship between obesity and asthma severity and control in adults. The Journal of allergy and clinical immunology. 2008;122(3):507-11.e6.

280. Devouassoux G, Levy P, Rossini E, Pin I, Fior-Gozlan M, Henry M, et al. Sleep apnea is associated with bronchial inflammation and continuous positive airway pressure-induced airway hyperresponsiveness. The Journal of allergy and clinical immunology. 2007;119(3):597-603.
281. Yigla M, Tov N, Solomonov A, Rubin AH, Harlev D. Difficult-to-control asthma and obstructive sleep apnea. The Journal of asthma : official journal of the Association for the Care of Asthma. 2003;40(8):865-71.
282. Lafond C, Series F, Lemiere C. Impact of CPAP on asthmatic patients with obstructive sleep apnoea. The European respiratory journal. 2007;29(2):307-11.
283. Miles JF, Garden GM, Tunnicliffe WS, Cayton RM, Ayres JG. Psychological morbidity and coping skills in patients with brittle and non-brittle asthma: a case-control study. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1997;27(10):1151-9.
284. Nouwen A, Freeston MH, Labbe R, Boulet LP. Psychological factors associated with emergency room visits among asthmatic patients. Behavior modification. 1999;23(2):217-33.
285. Chetta A, Gerra G, Foresi A, Zaimovic A, Del Donno M, Chittolini B, et al. Personality profiles and breathlessness perception in outpatients with different gradings of asthma. American journal of respiratory and critical care medicine. 1998;157(1):116-22.
286. Mancuso CA, Peterson MG, Charlson ME. Effects of depressive symptoms on health-related quality of life in asthma patients. Journal of general internal medicine. 2000;15(5):301-10.
287. Bucknall CE, Slack R, Godley CC, Mackay TW, Wright SC. Scottish Confidential Inquiry into Asthma Deaths (SCIAD), 1994-6. Thorax. 1999;54(11):978-84.
288. Heaney LG, Conway E, Kelly C, Gamble J. Prevalence of psychiatric morbidity in a difficult asthma population: relationship to asthma outcome. Respiratory medicine. 2005;99(9):1152-9.
289. Hasler G, Gergen PJ, Kleinbaum DG, Ajdacic V, Gamma A, Eich D, et al. Asthma and panic in young adults: a 20-year prospective community study. American journal of respiratory and critical care medicine. 2005;171(11):1224-30.
290. Nowobilski R, Furgal M, Czyz P, De Barbaro B, Polczyk R, Bochenek G, et al. Psychopathology and personality factors modify the perception of dyspnea in asthmatics. The Journal of asthma : official journal of the Association for the Care of Asthma. 2007;44(3):203-7.
291. Lehrer PM, Karavidas MK, Lu SE, Feldman J, Kranitz L, Abraham S, et al. Psychological treatment of comorbid asthma and panic disorder: a pilot study. Journal of anxiety disorders. 2008;22(4):671-83.
292. Fleming SL, Pagliari C, Churchill R, Shuldham CM, McKean M. Psychotherapeutic interventions for adults with asthma. The Cochrane database of systematic reviews. 2004(1):Cd002982.
293. Newman KB, Mason UG, 3rd, Schmaling KB. Clinical features of vocal cord dysfunction. American journal of respiratory and critical care medicine. 1995;152(4 Pt 1):1382-6.
294. Traister RS, Fajt ML, Whitman-Purves E, Anderson WC, Petrov AA. A retrospective analysis comparing subjects with isolated and coexistent vocal cord dysfunction and asthma. Allergy and asthma proceedings. 2013;34(4):349-55.
295. Boulet LP, Lemiere C, Archambault F, Carrier G, Descary MC, Deschesnes F. Smoking and asthma: clinical and radiologic features, lung function, and airway inflammation. Chest. 2006;129(3):661-8.

296. Tonnel AB, Tillie-Leblond I. [Refractory asthma: diagnosing allergic bronchopulmonary aspergillosis]. Presse medicale (Paris, France : 1983). 2008;37(1 Pt 2):161-6.
297. Sulaiman IM, E. Seheult, J. D'Arcy, S. Rapcan, V. Keane, J. Keane, MP. Murphy, D. Lane, SJ. Cushen, B. Mokoka, MC. Reilly, RB. Costello, RW. Inhaler Compliance Assessment (INCA) in an Astma Cohort. Irish Journal of Medical Science 2015;184(11):S520.
298. Holmes MS, D'arcy S, Costello RW, Reilly RB. Acoustic analysis of inhaler sounds from community-dwelling asthmatic patients for automatic assessment of adherence. IEEE journal of translational engineering in health and medicine. 2014;2:1-10.
299. Seheult JN, O'Connell P, Tee KC, Bholah T, Al Bannai H, Sulaiman I, et al. The Acoustic Features of Inhalation can be Used to Quantify Aerosol Delivery from a Diskus™ Dry Powder Inhaler. Pharmaceutical Research. 2014;31(10):2735-47.
300. Sulaiman I, Seheult J, MacHale E, D'Arcy S, Boland F, McCrory K, et al. Irregular and ineffective: a quantitative observational study of the time and technique of inhaler use. The Journal of Allergy and Clinical Immunology: In Practice. 2016;4(5):900-9. e2.
301. Sulaiman I, Seheult J, Sadasivuni N, MacHale E, Killane I, Giannoutsos S, et al. The Impact of Common Inhaler Errors on Drug Delivery: Investigating Critical Errors with a Dry Powder Inhaler. Journal of aerosol medicine and pulmonary drug delivery. 2017;30(4):247-55.
302. Seheult JN, Costello S, Tee KC, Bholah T, Al Bannai H, Sulaiman I, et al. Investigating the relationship between peak inspiratory flow rate and volume of inhalation from a Diskus Inhaler and baseline spirometric parameters: a cross-sectional study. Springerplus. 2014;3:496.
303. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-32.
304. Sulaiman I, Seheult J, MacHale E, Boland F, O'Dwyer SM, Rapcan V, et al. A Method to Calculate Adherence to Inhaled Therapy That Reflects the Changes in Clinical Features of Asthma. Ann Am Thorac Soc. 2016.
305. Zafari Z, Lynd LD, FitzGerald JM, Sadatsafavi M. Economic and health effect of full adherence to controller therapy in adults with uncontrolled asthma: A simulation study. Journal of Allergy and Clinical Immunology. 2014;134(4):908-U522.
306. Murphy C, Bennett K, Fahey T, Shelley E, Graham I, Kenny RA. Statin use in adults at high risk of cardiovascular disease mortality: cross-sectional analysis of baseline data from The Irish Longitudinal Study on Ageing (TILDA). BMJ Open. 2015;5(7):e008017.
307. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma. New England Journal of Medicine. 2009;360(10):973-84.
308. Cushen B, Sulaiman I, Greene G, MacHale E, Mokoka M, Reilly RB, et al. The Clinical Impact of Different Adherence Behaviors in Patients with Severe Chronic Obstructive Pulmonary Disease. American journal of respiratory and critical care medicine. 2018;197(12):1630-3.

Appendix 1: Literature search criteria

Electronic search: electronic search was conducted from 25th November 2015 till 25th January 2016. An updated search was conducted on the 21st June 2017 to include articles published between 1st December 2015 and 30th June 2017.

The MEDLINE strategy and RCT filter are adapted to identify trials in electronic databases.

#1 MeSH descriptor severe asthma Explode All

#2 severe asthma

#3 brittle asthma

#4 uncontrolled asthma

#5 'refractory' asthma

#6 difficult to treat asthma

#7 poorly controlled asthma

#8 steroid dependent asthma

#9 irreversible asthma

#10 #2 or #3 or #4 or #5 or #6 or #7 or #8 AND #10

Filter to identify randomised controlled trials (RCTs)

1. exp "clinical trial [publication type]"/

2. (randomized or randomised). ab, ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly. Ab, ti.

6. trial. Ab, ti.

7. groups. Ab, ti.

8. or/1-7

9. Animals/

10. Humans/

11. 10 not 9

Appendix 2: Characteristics of included studies

Study reference	Ayres (Omalizumab) 2004
Study title	Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma
Study duration	52 weeks
Trial registration:	Not documented
Study Population	Participants: omalizumab group, n = 206; best standard care (BSC) alone group, n=106 Eligibility criteria: patients' age 12–75 years, with persistent (>2 years) moderate-to-severe allergic asthma (according to the NHLBI guidelines), whose disease was poorly controlled. Poor control was defined as ≥1 emergency room visit/hospitalization and ≥1 additional course of oral corticosteroids because of asthma in the last year
Setting	49 centres in five European countries; France, n = 10; Germany, n = 9; Spain, n= 7; Switzerland, n =3; United Kingdom, n =20
Interventions	BSC with or without subcutaneous omalizumab for 12 months
Adherence reported	No
Primary outcomes	The annualised number of asthma deterioration-related incidents (ADRIs)

Secondary outcomes	Annualized number of clinically significant asthma exacerbations, morning FEV1, use of rescue salbutamol, and Wasserfallen asthma symptom score

Study reference	Bardelas (Omalizumab) 2012
Study title	A 26-week, randomized, double-blind, placebo-controlled, multicentre study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma
Study duration	2-week screening period. 24 weeks
Trial registration:	NCT00267202
Study Population	Participants: omalizumab group, n= 136; control group, n= 135 Eligibility criteria: patients' age ≥12 years; inadequately controlled persistent allergic asthma (ACT total score of ≤19); treated with Step 4 or higher asthma maintenance therapy(ICS + LABA/leukotriene receptor antagonist/theophylline/zileuton) according to the 2007 NHLBI guidelines; total serum IgE 30 to 700 IU/mL. One or more of the following with four weeks of screening phase: symptoms > 2 days/week; night-time awakenings ≥ 1 time/week; use of SABA > 2 days/week; FEV1 ≤ 80% predicted; background inhaled steroid dose: at least 250 mcg fluticasone twice daily or 320 mcg budesonide twice daily
Setting	United States
Interventions	Omalizumab administered subcutaneously based on body weight and serum IgE; 150 or 300 mg every four weeks or 225, 300 or 375

	mg every two weeks versus placebo with same inactive ingredients as study drug for 24 weeks
Adherence reported	No
Primary outcomes	The change from baseline to week 24 in ACT total score
Secondary outcomes	The change from baseline to week 24 for the following outcomes; the Investigator's Global Evaluation of Treatment Effectiveness (IGETE). Work productivity and activity impairment questionnaire–asthma (WPAI-A), electronic diaries, FEV1, use of rescue corticosteroids, safety assessment

Study reference	Beeh (Tiotropium) 2014
Study title	Tiotropium Respimat in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma
Study duration	4-week run-in period. 16 weeks of treatment phase and 3 weeks follow up period
Trial registration:	NCT01233284
Study Population	Participants: crossover trial, 149 patients randomised Eligibility criteria: Male or female patients aged 18–75 years, with at least a 3-month history of asthma at the time of enrolment and an initial diagnosis of asthma made before the age of 40 years. Asthma maintenance treatment; stable medium-dose ICS (400–800µg budesonide or equivalent), alone or in a fixed-dose combination with a LABA or short-acting β2-agonist, for at least 4 weeks prior to Visit 1. A diagnosis of asthma confirmed at Visit 1 was required with bronchodilator reversibility (15–30 minutes after 400µg salbutamol) of ≥12% and ≥200 mL; ACQ-7 mean score of ≥1.5 at Visits 1 and 2, to have a pre-bronchodilator FEV1 of ≥60% and ≤90% of predicted normal FEV1 at Visit 1, and to demonstrate absolute FEV1 variability within 30% between Visits 1 and 2
Setting	19 sites in three European countries; Germany, Austria and Ukraine
Interventions	tiotropium 5µg, 2.5µg or 1.25µg or placebo, all delivered via the Respimat® Soft Mist™ inhaler for 16 weeks
Adherence reported	No

Primary outcomes	Peak FEV1 measured within the first 3 hours after dosing, after every 4-week treatment period
Secondary outcomes	Trough FEV1; peak FVC within the first 3 hours after dosing (FVC)(0-3h); trough FVC; FEV1 area under the curve (AUC) within the first 3 hours after dosing {FEV1 AUC(0-3h)}; FVC AUC(0-3h); pre-dose PEF morning and PEF evening ACQ-7 at the end of every 4-week treatment period

Study reference	Berry (Etanercept) 2006
Study title	Evidence of a role of tumour necrosis factor α in 'refractory' asthma
Study duration	24 weeks
Trial registration:	NCT00276029
Study Population	Participants: Crossover trial, 30 patients were randomised Eligibility criteria: Patients with 'refractory' asthma, as per ATS criteria with the exception that the daily dose of ICS required to meet the definition was modified to >2000μg of beclomethasone or its equivalent to reflect European practice
Setting	Leicester, United Kingdom
Interventions	Placebo (1 ml of 0.9% saline) or etanercept (25 mg made into a 1-ml solution with the addition of the manufacturer's diluent) was administered subcutaneously twice weekly
Adherence reported	Yes
Primary outcomes	The difference in the change in the PC20 from 0 to 10 weeks between the placebo and etanercept treatment phases and the difference in the change in the asthma quality-of-life score from 0 to 10 weeks between the treatment phases
Secondary outcomes	The net change in post-bronchodilator FEV1, FEF25–75, and FVC; symptom scores; exhaled nitric oxide concentrations; computed alveolar nitric oxide concentrations; differential inflammatory cell counts in sputum; and mediator concentrations in sputum supernatant

Study reference	Bel Mepolizumab 2014
Study title	Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma
Study duration	3-8-week run-in period. 32 weeks
Trial registration:	NCT01691508
Study Population	Participants: mepolizumab group, n=69; placebo group, n=66 Eligibility criteria: at least a 6-month history of maintenance treatment with systemic glucocorticoids (5 to 35 mg per day of prednisone or its equivalent) before entering the study; high-dose inhaled glucocorticoids and an additional controller; blood eosinophil level of either ≥ 300 cells/µL during the 12-month period before screening or ≥150 cells/µL during the optimization phase
Setting	Amsterdam, Australia and United Kingdom
Interventions	Mepolizumab 100mg or placebo was administered subcutaneously once every 4 weeks until week 20
Adherence reported	No
Primary outcomes	Percentage reduction in the daily oral glucocorticoid dose during weeks 20 to 24 as compared with the dose determined during the optimization phase
Secondary outcomes	Proportions of patients who had a reduction of 50% or more in the oral glucocorticoid dose, who had a reduction in the oral glucocorticoid dose to a value of ≤5.0 mg per day, and who had a total cessation in oral glucocorticoid use; the median percentage reduction in the oral glucocorticoid dose; annualised rates of

	asthma exacerbations; the mean change from baseline in the FEV1 before and after bronchodilation; ACQ-5 score; SGRQ score; safety; immunogenicity

Study reference	Bjermer (Reslizumab) 2016
Study title	Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study
Study duration	20 weeks
Trial registration:	NCT01270464
Study Population	Participants: reslizumab 0.3mg/kg group, n=104; reslizumab 3.0mg/kg group, n= 106; placebo group, n=104 Eligibility criteria stated as: patients of the age 12-75 years with moderate-severe asthma, inadequately controlled (ACQ-7 score ≥1.5), airway reversibility (≥12% to SABA), were receiving treatment with at least a medium-dose ICS (fluticasone propionate ≥440 µg/day or equivalent) and had at least one blood eosinophil count of ≥400 cells/µL during the screening period
Setting	68 locations across 13 countries
Interventions	IV infusion of reslizumab 0.3 mg/kg, reslizumab 3.0 mg/kg, or placebo once every 4 weeks (total of 4 doses)
Adherence reported	Yes

Primary outcomes	Improvement in prebronchodilator FEV1 compared with placebo over 16 weeks
Secondary outcomes	FVC, ACQ-5, Asthma Symptom Utility Index (ASUI19), AQLQ, rescue inhaler use, and blood eosinophil levels over 16 weeks

Study reference	Bleecker (Benralizumab) 2016
Study title	Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial
Study duration	48 weeks
Trial registration:	NCT01928771
Study Population	Participants: benralizumab 30 mg 4 weekly group, n=399; benralizumab 30 mg 8 weekly group, n=398; or placebo group, n=407 Eligibility criteria: ≥ 2 exacerbations in the previous 12 months; ACQ-6 score ≥ 1.5 at enrolment FEV1 < 80% (if 12-17 years old, < 90%); maintenance treatment with high-dose (≥ 500µg/d FP or equivalent) ICS/LABA for ≥ 12 months for adults > 18 years, or at least medium-dose (≥ 250µg/d FP or equivalent) ICS/LABA for children (12-17 years)
Setting	374 sites in Australia, Brazil, Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russia, South Africa, South Korea, Spain, Turkey, the UK, the USA, and Vietnam
Interventions	SC benralizumab 30 mg/mL every 4 weeks or every 8 weeks versus placebo
Adherence reported	Yes
Primary outcomes	Annual asthma exacerbation rate at week 48 weeks

Secondary outcomes	Prebronchodilator FEV1 and total asthma symptom score (a composite of daytime and night-time symptoms scored 0–6 overall) at week 48

Study reference	Brightling (Tralokinumab) 2015
Study title	Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial
Study duration	5-week screening and run-in period. 52 weeks
Trial registration:	NCT01402986
Study Population	Participants: tralokinumab 2 weekly group, n=150 or 4 weekly group, n=151 or placebo group, n=151 Eligibility criteria: patients of the age 18–75 years with severe uncontrolled asthma, consistent with the ERS/ATS definition, who were receiving high dose ICS (total daily dose >500µg fluticasone dry powder inhaler or equivalent via metered dose inhaler) plus a LABA at least 30 days before visit 1 (run-in day –35), and who had at least two, but no more than six, exacerbations in the previous 12 months.
Setting	98 sites in North America, South America, Europe, and Asia
Interventions	Placebo or tralokinumab administered subcutaneously either every 2 weeks to week 50, or every 2 weeks for 12 weeks followed by every 4 weeks to week 48
Adherence reported	Yes
Primary outcomes	Annual asthma exacerbation rate at week 52 weeks
Secondary outcomes	Change in FEV1, FVC, IC, and PEF, EQ-5D; at week 52

Study reference	Brinke (IM triamcinolone) 2004
Study title	"'refractory'" eosinophilic airway inflammation in severe asthma effect of parenteral corticosteroids
Study duration	2 weeks
Trial registration:	Not specified
Study Population	Participants: triamcinolone group, n= 22, placebo group, n=11 Eligibility criteria: patients of the age 21–73 years; clinically stable for at least 4 weeks; percentage sputum eosinophils above the upper limit of normal (2%); beclomethasone dose of 1,600–6,400 g/day or equivalent and LABA for more than 1 year and had had at least one (median, 4; range, 1–7) course of oral corticosteroids during the past year or 5 mg or more of oral prednisone daily.
Setting	Amsterdam and Netherlands
Interventions	One single intramuscular injection of 3 ml (40 mg/ml) long-acting triamcinolone acetonide (Kenacort-A40; Bristol-Myers Squibb, Woerden, The Netherlands) or matched placebo (3 ml NaCl 0.9%) was given.
Adherence reported	No
Primary outcomes	Not specified
Secondary outcomes	Sputum and peripheral blood eosinophil /neutrophil counts, FEV1, exhaled nitric oxide

Study reference	Brusselle (Azithromycin) 2013
Study title	Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial
Study duration	2-week run-in period. 26 weeks
Trial registration:	NCT00760838
Study Population	Participants: azithromycin group, n=55; placebo group, n=54 Eligibility criteria: patients of the age 18–75 years, with a diagnosis of persistent asthma, a history consistent with Global Initiative for Asthma step 4 or 5 clinical features, received high doses of inhaled corticosteroids (≥1000 mg fluticasone or equivalent) plus inhaled long-acting β2 agonists for at least 6 months prior to screening and had had at least two independent severe asthma exacerbations requiring systemic corticosteroids and/or LRTI requiring antibiotics within the previous 12 months.
Setting	Belgium
Interventions	Capsules with 250 mg azithromycin (prepared from capsules of Zitromax) or placebo. After randomisation, the patients took one capsule per day for 5 days and then one capsule three times a week.
Adherence reported	Yes
Primary outcomes	The rate of severe asthma exacerbations and/or LRTI requiring antibiotics during the 26-week treatment phase

Secondary outcomes	Pre- and post-bronchodilation FEV1 morning and evening peak expiratory flow (PEF), AQLQ score and (ACQ score). All secondary outcomes were ascertained at visits 2, 3, 4, 5 and 6 (at randomisation and weeks 4, 10, 18 and 26 of the treatment period), except for the questionnaires which were completed by the patient at visits 2, 4 and 6 only.

Study reference	Busse (Omalizumab) 2001
Study title	Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma
Study duration	4-6-week run-in period. 28 weeks
Trial registration:	Not specified
Study Population	Participants: Omalizumab group, n= 268; Placebo group, n=257 Eligibility criteria: patients of the age 12–75 years; Male or female symptomatic allergic asthmatics despite treatment with ICS; duration of asthma, ≥1 year; positive immediate responses on skin prick testing to at least 1 common allergen, including Dermatophagoides farinae, Dermatophagoides pteronyssinus, cockroach (whole body), dog, or cat; total serum IgE ≥30 IU/mL to ≤700 IU/mL; FEV1 reversibility of ≥12% within 30 minutes after administration of albuterol (90-180 μg); baseline FEV1 ≥40% and ≤80% of predicted; and treatment with 420 to 840 μg/day of beclomethasone dipropionate or its equivalent ICS for ≥3 months prior to randomization
Setting	United States and United Kingdom
Interventions	Placebo or omalizumab administered subcutaneously every 2 or 4 weeks, depending on baseline IgE level and body weight.
Adherence reported	No
Primary outcomes	Number of exacerbation episodes experienced by a patient during the steroid reduction period (4 months) and during the stable steroid phase (3 months)

Secondary outcomes	Number of patients experiencing at least 1 exacerbation; daily asthma symptoms; rescue medication use; pulmonary function; and global evaluation of treatment effectiveness (time frame at week 16 and week 28)

Study reference	Busse (Brodalumab) 2013
Study title	randomized, double-blind, placebo-controlled study of brodalumab, a human anti–il-17 receptor monoclonal antibody, in moderate to severe asthma
Study duration	4-week run-in period. 12 weeks
Trial registration:	NCT01199289
Study Population	Participants: Brodalumab Q2W 140 mg group, n=74; 210 mg group, n= 76; 280 mg group, n =76; placebo group, n = 76 Eligibility criteria: patients of the age 18–65 years with inadequately controlled (ACQ≥1.5, ≥50% to ≤ 80% predicted FEV1, and ≥12% reversibility over baseline FEV1 with SABA inhalation) physician diagnosed moderate to severe asthma on stable ICS (>200 and <1,000 mg/d of fluticasone powder or equivalent for >3 month before screening, and had to be on a stable dose for >30 days) with or without additional LABAs
Setting	47 sites in 10 countries; Austria, Belgium, Canada, Finland, Hungary, Netherlands, Poland, Russia, South Korea, and the United States
Interventions	Brodalumab (140, 210, 280 mg) or placebo subcutaneously at day 1 and weeks 1, 2, 4, 6, 8, and 10
Adherence reported	No
Primary outcomes	The total change in ACQ-7 score from baseline to Week 12

Secondary outcomes	Changes from baseline to week 12 in pre- and post-bronchodilator FEV1, morning PEF, rescue SABA use, daily asthma symptom score, and symptom-free days

Study reference	Busse (Daclizumab) 2008
Study title	Daclizumab improves asthma control in patients with moderate to severe persistent asthma a randomized, controlled trial
Study duration	2-5 weeks run-in period. 20 weeks of treatment period and 16 weeks of follow up
Trial registration:	NCT00028288
Study Population	Participants: Daclizumab group, n=88; placebo group, n= 27 Eligibility criteria: non-smoking adults with asthma; 18–70 years old; asthma history of 6 months or longer; FEV1 of 50–80% of predicted; reversibility of at least 12% with inhaled short-acting β2- agonist; at least 1,200 mg daily inhaled triamcinolone acetate acetonide (or equivalent ICS) for 3 months or more before enrolment
Setting	24 centres in the United States
Interventions	Daclizumab (intravenous loading dose, 2 mg/kg, then 1 mg/kg) or placebo every 2 weeks, added to stable-dose triamcinolone acetate acetonide through week 12
Adherence reported	No
Primary outcomes	Percent change in FEV1 from randomization to day 84
Secondary outcomes	Asthma exacerbations, time to asthma exacerbation, morning/evening PEF, rescue medication use, daytime/ night-time asthma symptoms, and asthma-free days from randomization to day 84

Study reference	Busse (AMG 853) 2012
Study title	Safety and efficacy of the prostaglandin D2 receptor antagonist AMG 853 in asthmatic patients
Study duration	4-weeks run-in period. 12 weeks
Trial registration:	Not documented
Study Population	Participants: 200 mg of AMG 853 n=80 ; 100 mg of AMG 853 n= 79; 25 mg of AMG 853, n= 79; 5 mg of AMG 853, n=80; placebo group, n= 79 Eligibility criteria: patients of the age 18 to 65 years; moderate-to-severe asthma, with ongoing asthma symptoms {ACQ scores of ≥1.5 at screening and baseline, or FEV1 of ≥50% and ≤80% at screening, and at least 12% reversibility over baseline FEV1 with SABA; ≤8 puffs or nebulized equivalent (≤2 treatments with 2.5 mg of albuterol)} and were receiving stable inhaled corticosteroids (ICSs; ≥200 and ≤1000 mg/day fluticasone or equivalent) for 30 or more days, with consecutive use for at least the prior 3 months before screening
Setting	73 centres in the United States, Canada, and Europe
Interventions	Oral placebo; 5, 25, or 100 mg of AMG 853 twice daily; or 200 mg of AMG 853 once daily
Adherence reported	No
Primary outcomes	The change in ACQ symptom scores from baseline to week 12

Secondary outcomes	The change from baseline to week 12 in prebronchodilator and postbronchodilator FEV1 (percentage change), morning and evening PEFR, frequency of rescue SABA use, daily asthma symptoms, AQLQ scores, and the proportion of symptom-free days over the treatment period. The incidence of asthma exacerbations was evaluated as an exploratory end point. Other exploratory end points included fraction of exhaled nitric oxide (FENO) and induced sputum eosinophil numbers (sub study). Blood eosinophil numbers and serum IgE levels

Study reference	Cahill (Imatinib) 2017
Study title	KIT inhibition by imatinib in patients with severe 'refractory' asthma
Study duration	4-week run-in period. 24weeks
Trial registration:	NCT01097694
Study Population	Participants: Imatinib group, n=32 ; placebo group n= 30 Eligibility criteria: patients of the age 18–55 years, diagnosed with asthma for at least 1 year; 'refractory' asthmatics, defined as reporting that their asthma has not been completely controlled in the past 3 months despite continuous treatment with high dose ICS (fluticasone ≥ 1000 mg or equivalent) and LABA, with or without continuous OCS; uncontrolled asthma(ACQ ≥ 1.5) during the run-in period; FEV1 > 55% predicted; methacholine PC20 < 4 mg/ml; > 80% compliance with peak flow recording and diary completion during the screening period
Setting	7 centres in the United States
Interventions	Imatinib or placebo once daily for 24 weeks. Imatinib treatment was initiated at an oral dose of 200 mg per day for 2 weeks, after which the dose was increased to 400 mg per day
Adherence reported	Yes
Primary outcomes	The change in airway hyperresponsiveness, assessed as PC20, from baseline to 3 and 6 months of therapy in the imatinib group as compared with the corresponding changes in the control group

Secondary outcomes	Airway physiological outcomes, computed tomography bronchial wall thickness and patient reported outcomes: (from baseline to 3 and 6 months): FEV1, morning and evening PEF, maximum FEV1 post-bronchodilator (FEV1 after 4-8 puffs albuterol), Adenosine Monophosphate (AMP), PC20, use of as needed rescue medication, ACQ scores, AQLQ, score, symptom free days, asthma exacerbations

Study reference	Castro (Bronchial thermoplasty) 2010
Study title	Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma a multicentre, randomized, double-blind, sham-controlled clinical trial
Study duration	52 weeks
Trial registration:	NCT00231114
Study Population	Participants: Bronchial thermoplasty (BT) group, n=190; sham group, n= 98 Eligibility criteria: adults (18–65 years of age) diagnosed with asthma who required regular maintenance medications of ICS (1,000 mg/d beclomethasone or equivalent) and LABA >100 mg/d salmeterol or equivalent) for at least 4 weeks before entry; baseline AQLQ score ≤6.25; prebronchodilator FEV1 >60% of predicted, airway hyperresponsiveness (methacholine PC20 ,8 mg/ml), at least 2 days of asthma symptoms during the 4-week baseline period, and being a non-smoker for at least 1 year with less than 10 pack-years smoking history.
Setting	30 investigational sites in six countries; United States, United Kingdom, Canada, Brazil, Netherlands, Australia
Interventions	BT or the sham group. The bronchoscopy procedures were performed 3 weeks apart
Adherence reported	No

Primary outcomes	The difference between study groups in the AQLQ score change from baseline to the average of the 6-, 9-, and 12-month scores (integrated AQLQ)
Secondary outcomes	ACQ scores, percentage of symptom-free days, symptom scores, morning PEF, rescue medication use, and FEV1, the numbers of severe asthma exacerbations, the percentage of subjects experiencing severe exacerbations, respiratory-related unscheduled physician office visits, emergency department (ED) visits, hospitalizations, and days missed from work/school or other activities due to asthma

Study reference	Castro (Benralizumab) 2014
Study title	Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study
Study duration	52 weeks
Trial registration:	NCT01238861
Study Population	Participants: 324 eosinophilic patients: benralizumab 2 mg dose, n=81; 20 mg dose, n=81;100 mg dose, n=82; placebo group, n=80: 285 non-eosinophilic patients : 100 mg benralizumab n=142; placebo group, n=143 Eligibility criteria: 2–6 exacerbations in the previous 12 months, ACQ-6 score ≥ 1.5 at least twice during screening, morning pre-bronchodilator FEV1 40%–90% maintenance treatment with medium- to high-dose ICS in combination with LABA for ≥ 12 months
Setting	33 sites in the United States, Canada, Bulgaria, Brazil, Peru, Mexico, Poland, Russia, Argentina, and Colombia
Interventions	6 arms: benralizumab 2 mg or benralizumab 20 mg or benralizumab 100 mg or placebo delivered by 2 SC injections every 4 weeks for the first 3 doses (weeks 1, 4, and 8), then every 8 weeks (weeks 16, 24, 32, and 40)
Adherence reported	No
Primary outcomes	Asthma annual exacerbation rate in eosinophilic individuals, calculated as the total number of reported exacerbations in each

	group up to week 52 divided by the total duration of person-year follow-up in each group
Secondary outcomes	The change from baseline in FEV1, mean ACQ-6 score, overall symptom score, and mean AQLQ score at week 52. Exploratory endpoints included change in FeNO, and blood eosinophil counts

Study reference	Castro (Reslizumab) 2015
Study title	Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials
Study duration	48 weeks
Trial registration:	NCT01287039 (study 1) and NCT01285323 (study 2)
Study Population	Participants: Study 1; reslizumab group, n=245; placebo group, n=244 Study 2: reslizumab group n= 232; placebo group, n=232 **Eligibility criteria:** patients with moderate-severe asthma, ACQ-7 score ≥ 1.5; maintenance treatment with medium-dose ICS (i.e. ≥ 440 µg/d FP or equivalent daily); ± additional controller or maintenance OCS and at least 1 exacerbation in the past 12 months); blood eosinophils ≥ 400 cells/µL during 2-4 week screening period
Setting	128 clinical research centres in study 1 and 104 centres in study 2 from Asia, Australia, North America, South America, South Africa, and Europe
Interventions	IV infusion of reslizumab 3 mg/kg or matching placebo every 4 weeks (13 doses with last dose in week 48)
Adherence reported	No
Primary outcomes	The frequency of clinical asthma exacerbations per patient during the 52-week treatment period

Secondary outcomes	The change from baseline in FEV1, ACQ-7 score,21,25 ASUI score, rescue use of short-acting β-agonist, and blood eosinophil count to each scheduled visit; AQLQ total score were assessed at weeks 16, 32, and 52

Study reference	Castro (Reslizumab) 2011
Study title	Reslizumab for poorly controlled, eosinophilic asthma a randomized, placebo-controlled study
Study duration	15 weeks
Trial registration:	Not documented
Study Population	Participants: reslizumab group, n= 53; placebo group, n=53 Eligibility criteria**:** patients of the age 18–75 years with a diagnosis of asthma confirmed by airway hyperreactivity (a ≥20% reduction in FEV1 after administration of methacholine up to 16 mg/ml) or by airway reversibility (a >12% improvement in FEV1 after administration of a beta-agonist); treated with high-dose ICS (>440 mg of fluticasone twice per day) in combination with at least one other agent (including SABA, leukotriene antagonists, and cromolyn sodium); that was poorly controlled as indicated by an ACQ score of ≥1.5 and associated with induced sputum eosinophils of ≥3%
Setting	25 sites in the United States and Canada
Interventions	to infusions of reslizumab (3.0 mg/kg) or placebo (0.9% saline) at a 1:1 ratio at baseline and at Weeks 4, 8, and 12
Adherence reported	No
Primary outcomes	The difference between the reslizumab and placebo groups in the change from baseline to end of therapy (Week 15 or early withdrawal) in the ACQ score

Secondary outcomes	Spirometry, blood and induced sputum eosinophil counts, and the percentage of patients with clinical asthma exacerbations

Study reference	Chanez (Omalizumab) 2010
Study title	Omalizumab-induced decrease of Fc3RI expression in patients with severe allergic asthma
Study duration	16 weeks
Trial registration:	NCT00454051
Study Population	Participants: omalizumab group, n= 20; control group: n=11 Eligibility criteria: adults aged ≥ 18 years; participants with severe persistent allergic asthma with the following characteristics: FEV1 < 80% of predicted; frequent daily symptoms (≥ four days/week on average) or nocturnal awakening (≥ one/week on average); multiple severe asthma exacerbations: either ≥ two severe asthma exacerbations requiring an unscheduled medical intervention with systemic corticosteroid in the past year, or hospitalisation (including emergency room treatment) for an asthma exacerbation in the past year, despite a high-dose ICS > 1000 mg beclomethasone dipropionate or equivalent and LABA; an allergy to a perennial allergen demonstrated with convincing criteria {i.e. positive prick skin test or in vitro reactivity to a perennial aeroallergen (RAST)}; total serum IgE level ≥ 30 to ≤ 700 IU/mL and suitable serum total IgE level; weight according to Xolair dosing tablets
Setting	France
Interventions	Omalizumab injected subcutaneously every two weeks or every four weeks for 16 weeks (dose and dosing interval determined based on participant body weight and pre-treatment serum IgE level) versus placebo

Adherence reported	No
Primary outcomes	The change (%) from baseline in FcεRI (high-affinity IgE receptor) expression on blood basophils and dendritic cells after 16 weeks of treatment with omalizumab as compared with placebo (time frame: baseline and week 16); change (%) from baseline in mean fluorescence intensity of FcεRI after 16 weeks of treatment with omalizumab as compared with placebo (time frame: baseline and week 16)
Secondary outcomes	The change (%) from baseline in percent of basophils and dendritic cells expressing FcεRI after 4, 8, 12 and 16 weeks of treatment (time frame: baseline, weeks 4, 8, 12 and 16); change (%) from baseline in mean fluorescence intensity of FcεRI after 4, 8, 12 and 16 weeks of treatment (time frame: baseline, weeks 4, 8, 12 and 16); change from baseline in the number of days with asthma symptoms per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of puffs of rescue medication per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of nights with awakenings per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of days with impairment in daily activities per week (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of days with absence from school or work due to asthma symptoms (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of days with hospitalisations (time frame:

	baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in the number of unscheduled clinic visits (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); change from baseline in morning daily peak expiratory flow (PEF) (time frame: baseline (four-week screening period before randomisation) and end of study (weeks 12 to 16)); physician's overall assessment of treatment effectiveness (time frame: after 16 weeks of treatment)

Study reference	Corren (AMG 317) 2010
Study title	A randomized, controlled, phase 2 study of AMG317, an il-4ra antagonist, in patients with asthma
Study duration	16 weeks
Trial registration:	NCT 00436670
Study Population	Participants: AMG 317 75 mg group, n =73; AMG 317 150 mg group, n = 73; AMG 317 300 mg group, n =72 ; placebo group, n=74 Eligibility criteria: patients of the age 18-65 years, with moderate to severe asthma, and receiving stable doses of inhaled corticosteroids (ICS) (>200 to <1,000 mg/d fluticasone or equivalent; ACQ score ≥1.5, FEV1% predicted of ≥50% to ≤80% at screening, and greater than or equal to 12% reversibility over baseline FEV1 with β2-agonist inhalation
Setting	United States
Interventions	AMG 317 (75 mg, 150 mg, or 300 mg) or placebo subcutaneously once weekly for 12 weeks
Adherence reported	No
Primary outcomes	The change in ACQ symptom score from baseline to Week 12.
Secondary outcomes	Changes in pre and post-bronchodilator FEV1, morning and evening PEFR, diurnal and interday variation of PEFR, rescue b-agonist use, and Asthma AQLQ score. Asthma exacerbations were also

	evaluated, and two definitions were used: (1) need for systemic steroids, or (2) need for systemic steroids or doubling of ICS dose

Study reference	Corren (Lebrikizumab) 2011
Study title	Lebrikizumab treatment in adults with asthma
Study duration	2-week run in period. 32 weeks
Trial registration:	NCT00930163
Study Population	Participants: lebrikizumab group, n=106; placebo group, n=112 Eligibility criteria: patients had asthma diagnosed by a physician { at least a 12% increase in the FEV1 after inhalation of a SABA, and prebronchodilator FEV1 between 40% and 80% (inclusive)}; the use for at least 6 months of inhaled glucocorticoids (≥200 and ≤1000 µg of inhaled fluticasone propionate daily, administered by means of a dry powder inhaler, or a nominal equivalent); evidence of uncontrolled asthma (ACQ-5 ≥1.5) on the day of randomization
Setting	United States
Interventions	Lebrikizumab 250 mg or placebo was given subcutaneously once a month for a total of 6 months
Adherence reported	Yes
Primary outcomes	The relative change in prebronchodilator FEV1 from baseline to week 12
Secondary outcomes	Rates of protocol- defined exacerbations and severe exacerbations through week 24, morning prebronchodilator peak exploratory flow, change in ACQ5 score from baseline to week 12, asthma symptom score as assessed by means of the ACDD, and use of rescue medication

Study reference	Corren (Reslizumab) 2016
Study title	Phase 3 study of reslizumab in patients with poorly controlled asthma effects across a broad range of eosinophil counts
Study duration	3-week screening period. 28 weeks
Trial registration:	NCT01508936
Study Population	Participants: reslizumab group, n=398; placebo group, n=98 Eligibility criteria**:** patients with moderate-severe asthma, inadequately controlled (ACQ-7 ≥ 1.5); maintenance treatment with medium-dose ICS
Setting	66 sites across the United States
Interventions	Reslizumab 3.0 mg/kg was given intravenously or placebo once every 4 weeks (total of 4 doses)
Adherence reported	No
Primary outcomes	The change in FEV1 from baseline to week 16
Secondary outcomes	ACQ-7 score14; rescue (SABA) use within the previous 3 days (assessed using 3-day recall at scheduled visits); FVC; and blood eosinophils (standard complete blood count) from baseline to week 16

Study reference	Cox (Bronchial thermoplasty) 2007
Study title	Asthma control during the year after bronchial thermoplasty
Study duration	52 weeks
Trial registration:	NCT00214526
Study Population	Participants: Bronchial thermoplasty (BT) group, n=56, control group n=56 Eligibility criteria**:** patients aged 18–65 years of age; moderate or severe persistent asthma, defined according to the GINA guidelines, requiring daily therapy with ICS equivalent to a dose of 200µg or more of beclomethasone and LABA, at a dose of 100µg or more of salmeterol (Serevent, GlaxoSmithKline) or the equivalent, to maintain reasonable asthma control; airflow obstruction, assessed as a prebronchodilator FEV1 of 60 to 85% of the predicted value, and airway hyperresponsiveness, defined by a provocative concentration of methacholine required to lower the FEV1 by 20% (PC20) of less than 8 mg/mL, as well as stable asthma during the 6 weeks before enrolment
Setting	11 centres in four countries; Canada, Brazil, UK and Denmark
Interventions	The BT group underwent three bronchoscopy procedures performed with the use of the Altair system at intervals of approximately 3 weeks. Control subjects had three treatment visits at intervals of 3 weeks for clinical review and spirometry assessment and received a systemic corticosteroid similar to that administered to subjects in the BT group

Adherence reported	No
Primary outcomes	The difference between the two groups in the change in the rate of mild exacerbations between baseline and later time point
Secondary outcomes	ACQ, PEF, AQLQ

Study reference	Coyle (Bosentan) 2013
Study title	The effect of the endothelin-1 Receptor antagonist, bosentan, on Patients with Poorly Controlled Asthma: A 17-week, Double-Blind, Placebo-Controlled Crossover Pilot Study
Study duration	7-10-day run-in period. 16weeks
Trial registration:	Not documented
Study Population	Participants: Bosentan group, n= 4 ; placebo group n= 3 Eligibility criteria: patients aged 21–70 years with a history of asthma, previously maintained on anti-inflammatory and long acting bronchodilator therapy (excluding tiotropium bromide), with a baseline FEV1% predicted of 40–70% and a minimum of 12% reversibility of FEV1 (after administration of albuterol) documented within the prior 2 years; poorly controlled asthma defined as symptoms including wheezing, chest tightness, or shortness of breath occurring at least three times a week or requiring use of "rescue" SABA at least three times a week
Setting	United States
Interventions	Bosentan 62.5 mg twice daily for 4 weeks followed by the therapeutic dose of bosentan 125 mg twice daily for an additional 4 weeks or identical shape and size placebo (crossover pilot study)
Adherence reported	No
Primary outcomes	The change in mean daily asthma symptom score between baseline and during the last week of bosentan 125 mg

Secondary outcomes	The change in ACT, change in FEV1 after therapy, albuterol use during the last week of therapy, and acute bronchodilator effect of bosentan as assessed by measuring change in FEV1 after bosentan 125 mg

Study reference	DeBoever (GSK679586) 2014
Study title	Efficacy and safety of an anti–IL-13 mAb in patients with severe asthma: A randomized trial
Study duration	4-week run-in period. 24weeks
Trial registration:	NCT00843193
Study Population	Participants: GSK679586 group, n=599; placebo group, n=599 Eligibility criteria: patients of the age 18 to 75 years with severe asthma, symptomatic (ACQ-7 score 1.5) while receiving ≥500µg/day fluticasone propionate or equivalent (FPE) and had a prebronchodilator FEV1 of 35% to 80% of predicted normal value with ≥12% reversibility on β-2-agonist inhalation; LABAs or OCSs (≤25 mg/d prednisolone or equivalent) were allowed
Setting	34 sites across 8 countries including United Kingdome and United States
Interventions	10 mg/kg GSK679586 intravenously or normal saline at day 1, week 4, and week 8
Adherence reported	No
Primary outcomes	The change from baseline in ACQ-7 score over 12 weeks
Secondary outcomes	The changes from baseline in free and total serum IL-13 levels, serum total IgE levels, and blood eosinophil counts were evaluated over the same time as exploratory end points

Study reference	Dente (Prednisolone) 2010
Study title	Effects of oral prednisone on sputum eosinophils and cytokines in patients with severe 'refractory' asthma
Study duration	2 weeks
Trial registration:	Not documented
Study Population	Participants: prednisone group, n=39; placebo group, n=20 Eligibility criteria: compliance with functional measurements and treatment, acceptable sputum samples, and no contraindications for the use of systemic corticosteroids; symptomatic asthma and a history of airway obstruction reversibility (a 12% increase in FEV1 of baseline value after 400 g of salbutamol); treated with 1,600 to 3,200 g/day of inhaled beclomethasone propionate or equivalent associated with LABA in the year preceding the study, ±additional controller therapy (oral leukotriene receptor antagonists, inhaled anticholinergics, oral theophylline, and regular low-dose oral corticosteroids)
Setting	Italy
Interventions	Oral prednisone (0.5 mg/kg daily) or placebo for 2 weeks, in addition to current regular treatment
Adherence reported	Yes
Outcomes	Outcomes: FEV1, PEFR, sputum eosinophil, sputum IL-5 and IL-8 level at 2weeks

Study reference	Erin (Infiliximab) 2006
Study title	The effects of a monoclonal antibody directed against tumor necrosis factor in asthma
Study duration	2–4-week run-in period. 12 weeks
Trial registration:	Not documented
Study Population	Participants: infliximab group, n=18; placebo group, n=20 Eligibility criteria: a mean total daily symptom score of at least 4 in the last 7 d of the run-in period (baseline period: Days 7 to 1), or at least 10% but less than 40% diurnal variation in peak PEF measured on at least 2 of 7 days in the same period
Setting	United Kingdom
Interventions	Infliximab (5 mg/kg) or placebo at Weeks 0 (Day 1), 2 (Day 15), and 6 (Day 43)
Adherence reported	No
Primary outcomes	The change from baseline (Days 7 to 1) to Week 8 (Days 50 to 56) in mean morning PEF, obtained from the patient diary data in the per protocol population
Secondary outcomes	The change from baseline (Days 7 to 1) to Week 8 (Days 50 to 56) in FEV1, asthma symptom scores, use of rescue SABA

Study reference	Fernandes (Prednisolone) 2014
Study title	Bronchodilator response as a hallmark of uncontrolled asthma: a randomised clinical trial
Study duration	10±5-day run-in period. 15± 5 days
Trial registration:	NCT00597064
Study Population	Participants: prednisolone group, n= 36; placebo group, n=35 Eligibility criteria: patients over 15 years old; non-smokers or ex-smokers (less than 5 packs/year); treated with ICS therapy (400 mcg Budesonide) plus LABA (12 mcg Formoterol) twice daily for at least 3 months (step 4 of GINA), exhibiting positive bronchodilator response (≥12% increase in post-bronchodilator FEV1 value compared to pre bronchodilator FEV1 value, and an increase in the absolute value of FEV1 of greater than 200 mL at the screening visit (V0), and controlled asthma by ACQ5 definition
Setting	Brazil
Interventions	Prednisone 40 mg daily or placebo for 2 weeks
Adherence reported	No
Outcomes assessed	Outcomes assessed: the change in FEV1, PEFR, sputum eosinophils and neutrophil counts at the final evaluation visit

Study reference	FitzGerald (Benralizumab) 2016
Study title	Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials
Study duration	56 weeks (final follow-up at 60 weeks).
Trial registration:	NCT01287039 (study 1) and NCT01285323 (study 2)
Study Population	Participants: 1306 participants enrolled. Allocation: eosinophil ≥ 300 cells per µL benralizumab 30 mg every four weeks, n=241; eosinophil ≥ 300 cells per µL benralizumab 30 mg Q8W, n=239; eosinophil ≥ 300 cells per µL placebo group, n= 248; eosinophil < 300 cells per µL benralizumab 30 mg every four weeks, n=116; eosinophil < 300 cells per µL benralizumab 30 mg Q8W, n=125; eosinophil < 300 cells per µL; placebo group, n=122 Eligibility criteria: patients with moderate-severe asthma; ≥ 2 exacerbations in the previous 12 months; ACQ-6 score ≥ 1.5 at enrolment; FEV1 < 80%; maintenance treatment with medium- (≥ 250 µg/day FP or equivalent) to high-dose (≥ 500 µg/day FP or equivalent) ICS/LABA for ≥ 12 months; high-dose ICS/LABA for ≥ 3 months
Setting	303 clinical research centres in the United States, Canada, Germany, Sweden, Poland, Romania, Ukraine, Argentina, Chile, Japan, and the Philippines
Interventions	Placebo or benralizumab 30 mg administered subcutaneously every 4 weeks for 56 weeks or every 4 weeks for 3 doses then 8 weeks thereafter for 56 weeks

Adherence reported	Yes
Primary outcomes	The frequency of clinical asthma exacerbations per patient during the 52-week treatment period, with events adjudicated by an independent review committee
Secondary outcomes	The pre-bronchodilator FEV1 and total asthma symptom score for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per μL, time to first asthma exacerbation; annual rate of asthma exacerbations associated with an emergency department visit, urgent care visit, or admission to hospital; post-bronchodilator FEV1; ACQ-6 score; and AQLQ score.

Study reference	Flood-Page (Mepolizumab) 2007
Study title	A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma
Study duration	4-week run-in period. 12 weeks treatment period and 8 weeks follow up period
Trial registration:	Not documented
Study Population	Participants: mepolizumab 750mg group n=116 ; mepolizumab 250mg group, n=120 ; placebo group, n=126 Eligibility criteria: non-smoking patients, aged 18–55 years, with asthma managed with ICS (maximum dose of beclomethasone dipropionate [BDP] or equivalent, 1,000 mg/d); FEV1% predicted of at least 50% and not >80% with documented b2-agonist reversibility of at least 12% after administration of 180 mg of albuterol (salbutamol); daily symptom score of at least 4 (maximum score, 12) during the 7 days preceding the baseline assessment
Setting	55 centres in five countries; France, Germany, the Netherlands, the United Kingdom, and the United States
Interventions	Mepolizumab (750 mg), mepolizumab (250 mg), or placebo
Adherence reported	No
Primary outcomes	The change from baseline in domiciliary morning PEF recorded at weeks 12 and 20
Secondary outcomes	The changes from baseline of FEV1, asthma summary symptom scores (the total of the daytime asthma, night-time asthma, and morning asthma scores), use of rescue medication such as albuterol

	(salbutamol), quality of life scores, asthma exacerbation rates, and eosinophil counts in blood and sputum

Study reference	Gao J-M (Montelukast) 2013
Study title	Montelukast improves air trapping, not airway remodelling, in patients with moderate-to-severe asthma: a pilot study
Study duration	2-week run-in period. 24 weeks
Trial registration:	NCT00699062
Study Population	Participants: salmeterol/fluticasone (SFC) plus Montelukast (SFC+M) group, n=19; salmeterol/fluticasone group, n=19 Eligibility criteria: patients of the age 16–65 years; FEV1 60%–80% predicted or less than 60% predicted
Setting	Beijing, China
Interventions	Salmeterol/fluticasone (SFC) alone or SFC plus Montelukast (SFC+M)
Adherence reported	No
Primary outcomes	The difference in the variables of small airways between the SFC group and SFC+M group after 24 weeks of treatment
Secondary outcomes	FEV1, FEV1% predicted FEV1/FVC), air trapping expressed by RV/TLC at 24 weeks with SFC alone or SFC+M

Study reference	Garcia (Omalizumab) 2013
Study title	A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma
Study duration	2-week screening period. 16 weeks
Trial registration:	NCT01007149
Study Population	Participants: omalizumab group, n= 20; placebo group, n=21 Eligibility criteria: patients aged 18 to 70 years with severe, persistent, nonatopic asthma that was uncontrolled according to the GINA guidelines despite daily high-dose ICS treatment (1,000 mg beclomethasone dipropionate or equivalent per day) plus a LABA with or without maintenance oral corticosteroid; at least two exacerbations requiring systemic corticosteroids, at least one hospitalization or ED visit in the year prior to randomization, or both; total serum IgE levels range: 30 to 700 IU/mL
Setting	10 centres in France
Interventions	Omalizumab or placebo subcutaneously every 2 weeks
Adherence reported	No
Primary outcomes	The change from baseline in FcЄRI expression on basophils and pDC2s at 16 weeks.
Secondary outcomes	Lung function, asthma control questionnaire scores, physician and patient global evaluation of treatment effectiveness (GETE), asthma exacerbation rates, and fraction of exhaled nitric oxide at 16 weeks

Study reference	Gevaert (Omalizumab) 2013
Study title	Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma
Study duration	2-week screening period. 16 weeks
Trial registration:	Not specified
Study Population	Participants: Omalizumab group, n=16; placebo group, n=8 Eligibility criteria: patients aged ≥ 18 years with CRSwNP (according to the European Position: Paper on Rhinosinusitis and Nasal Polyps guidelines) and comorbid asthma (based on GINA guidelines and diagnosed by a respiratory physician) for more than 2 years
Setting	Belgium
Interventions	Placebo or subcutaneous treatment with 2 weekly/8 injections in total or every month/4 injections in total) of omalizumab
Adherence reported	No
Primary outcomes	The reduction in total nasal endoscopic polyp score after 16 weeks
Secondary outcomes	The change in the following: sinus computed tomography scan, nasal and asthma symptoms, validated questionnaires (SF-36, RSOM-31 and AQLQ) and serum/nasal secretion biomarkers

Study reference	Girodet (Gallopamil) 2015
Study title	Calcium Channel Blocker Reduces Airway Remodelling in Severe Asthma A Proof-of-Concept Study
Study duration	3-month run-in period. 52 weeks
Trial registration:	NCT 00896428
Study Population	Participants: placebo group, n=15; Gallopamil group, n=16 Eligibility criteria: patients of the age ≥18 years with a clinical diagnosis of severe asthma according to ATS criteria, including characteristic symptoms (i.e., wheezing and breathlessness) and bronchial hyperresponsiveness confirmed either by a significant improvement by greater than 15% in the FEV1 10 minutes after the inhalation of 200 mg of salbutamol, or a provocative concentration of methacholine required to lower the FEV1 by 20% of less than 4 mg/ml
Setting	France
Interventions	100 mg of oral gallopamil hydrochloride twice daily or a matching placebo
Adherence reported	No
Primary outcomes	The bronchial smooth muscle (BSM) area assessed as the percentage of BSM surface on the whole bronchial sections surface at month 12
Secondary outcomes	Bronchial wall thickness, normalized BSM thickness, frequency of asthma exacerbations, ACQ, SABA use, AQLQ, FEV1, fractional exhaled nitric oxide (FENO), lung hyperinflation (VI950) or air

	trapping (VE850, difference or ratio between inspiratory and expiratory mean lung density), epithelial area, subepithelial membrane thickness, and lamina propria thickness at month 12

Study reference	Gotfried (Clarithromycin) 2004
Study title	effects of six-week clarithromycin therapy in corticosteroid-dependent asthma: a randomized, double-blind, placebo-controlled pilot study
Study duration	4-week of observation period. 14 weeks
Trial registration:	Not documented
Study Population	Participants: clarithromycin group, n=15; placebo group, n=6 Eligibility criteria: patients of the age 18 to 75 years with an established diagnosis of asthma and who had been receiving ~5 mg/d of prednisone for the preceding 6 months; stable asthma with a ~20% change in prednisone or bronchodilator dosage in the previous 4 weeks
Setting	USA
Interventions	Oral clarithromycin 500-mg tablets twice daily or identical placebo
Adherence reported	No
Outcomes	FVC, FEV1, FEV/FVC ratio, PEF, quality of life and asthma symptoms at the end of four weeks treatment

Study reference	Haldar (Mepolizumab) 2009
Study title	Mepolizumab and Exacerbations of 'refractory' Eosinophilic Asthma
Study duration	2-week run-in period. 50 weeks
Trial registration:	ISRCTN75169762
Study Population	Participants: mepolizumab 750 mg group, n=29; placebo group, n= 32 Eligibility criteria: ≥ 3% sputum eosinophils on at least 1 occasion in previous 2 years despite high-dose corticosteroid treatment; ≥ 2 exacerbations in previous 12 months; maintenance treatment with high-dose ICS
Setting	Single centre trial conducted at Institute for Lung Health, Leicester, UK
Interventions	Intravenous mepolizumab (750 mg) versus matched placebo (150 mL of 0.9% saline) at monthly intervals for 1 year
Adherence reported	No
Primary outcomes	The number of severe exacerbations per participant during the 50-week treatment phase
Secondary outcomes	Changes in eosinophil values in blood and sputum samples, FeNO, FEV1 (percent of the predicted value) after bronchodilator use, PC20, AQLQ score, symptom scores, computed assessment of airway-wall geometry, and bronchoscopic assessment of eosinophilic airway inflammation

Study reference	Hanania (Omalizumab) 2011
Study title	Omalizumab in Severe Allergic Asthma Inadequately Controlled with Standard Therapy
Study duration	2-4-week run-in period. 48 weeks
Trial registration:	NCT00314575
Study Population	Participants: omalizumab group: n=427; placebo group, n=423 (421 completed) Eligibility criteria: patients of the age 12 to 75 years with a history of severe allergic asthma for at least one year before screening; physician diagnosis of asthma on the basis of criteria specified by the NAEPP guidelines; uncontrolled asthma despite treatment with high-dose ICS and LABAs with or without other controllers (including OCS); baseline pre-bronchodilator FEV1 of 40% to 80% of predicted values; serum IgE level of 30 to 700 IU/mL and body weight of 30 to 150 kg; objective evidence of allergy to a relevant perennial aeroallergen, defined as a positive skin test result or in vitro response (radio-allergosorbent test) to dog, cat, cockroach, Dermatophagoides farinae (dust mite) or D. pteronyssinus documented in the 12 months before screening
Setting	193 sites in the United States and four sites in Canada
Interventions	Minimum dose of 0.008 mg/kg of body weight per IgE (IU/mL) every two weeks or 0.016 mg/kg per IgE (IU/mL) every four weeks versus placebo
Adherence reported	Yes

Primary outcomes	The rate of protocol-defined asthma exacerbations during the 48-week treatment period
Secondary outcomes	Change from baseline to week 48 in total asthma symptom severity score (TASS); change from baseline to week 48 in mean puffs per day of albuterol; and change from baseline to week 48 in overall asthma-specific health-related quality of life, as measured by the standardized version of the AQLQ score

Study reference	Hanania (Lebrikizumab) 2016
Study title	Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials
Study duration	2-week screening period, 52-weeks
Trial registration:	LAVOLTA; INCT01867125, and LAVOLTA II; NCT01868061
Study Population	Participants: 1081 patients were treated in LAVOLTA I and 1067 patients in LAVOLTA II Eligibility criteria: patients of the age 18–75 years with uncontrolled asthma, pre-bronchodilator FEV1 40–80% predicted, bronchodilator response of at least 12%, and on stable background therapy with ICS (500–2000µg per day fluticasone propionate or equivalent) for at least 6 months and at least one additional controller medication
Setting	United States, Canada, South Africa, Italy Czech Republic and Japan.
Interventions	Lebrikizumab 37.5 mg or 125 mg, or placebo subcutaneously, once every 4 weeks
Adherence reported	Yes
Primary outcomes	The rate of asthma exacerbations during the 52-week placebo-controlled period in biomarker-high patients (periostin ≥50 ng/mL or blood eosinophils ≥300 cells/µL, and including patients high in both)
Secondary outcomes	The absolute change in pre-bronchodilator FEV1 from baseline at week 52; time to first asthma exacerbation during the 52-week placebo-controlled period; rate of urgent asthma related health-

	care use during the 52-week placebo controlled period; absolute change in AQLQ from baseline at week 52; absolute change in asthma rescue medication use from baseline at week 52; and absolute change in asthma control, as measured by the ACQ-5, from baseline at week 52

Study reference	Hanania (Lebrikizumab) 2015
Study title	Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies
Study duration	No run-in period. 52 weeks
Trial registration:	LUTE study; NCT01545440 VERSE study; NCT01545453
Study Population	Participants: Lebrikizumab 37.5 mg group, n=117; Lebrikizumab 125 mg group, n=112; Lebrikizumab 250 mg group, n=118; placebo group, n=116 Eligibility criteria: a diagnosis of asthma ≥12 months; acute bronchodilator response (≥12% relative improvement) and pre-bronchodilator FEV1 40–80% of predicted; uncontrolled asthma (ACQ-5 score ≥1.5 and at least one of the following: symptoms >2 days/week, night-time awakenings ≥1 time/week, use of a SABA as rescue medication >2 days/week or interference with normal daily activities
Setting	United States
Interventions	Lebrikizumab 37.5, 125, 250 mg, or placebo subcutaneously every four weeks
Adherence reported	No
Primary outcomes	The rate of asthma exacerbations during the placebo-controlled period
Secondary outcomes	The change in prebronchodilator FEV1 from baseline, time to first asthma exacerbation during the placebo-controlled period, change from baseline in the

	AQLQ score, change in asthma rescue medication use from baseline, rate of urgent asthma-related healthcare use (i.e., hospitalisations, emergency department visits and acute care visits) during the placebo-controlled period

Study reference	Hedman (Methotrexate) 1996
Study title	Controlled trial of Methotrexate in patients with severe chronic asthma
Study duration	2-week run-in period. 24 weeks
Trial registration:	Not documented
Study Population	Participants: 13 patients enrolled, crossover trial Eligibility criteria: severe chronic asthma with continuous oral steroids treatment of at least 2.5mg/day for a year; Inhaled budesonide dose of ≥1.6mg; patient age <65years of age
Setting	Finland and Sweden
Interventions	15mg Methotrexate or identical placebo
Adherence reported yes/no	No
Outcomes	PEFR, FEV1

Study reference	Hodgson (Ciclesonide) 2015
Study title	A randomised controlled trial of small particle inhaled steroids in 'refractory' eosinophilic asthma (SPIRA)
Study duration	12 weeks
Trial registration:	NCT01171365
Study Population	Participants: ciclesonide group n=15; placebo group n=15 Eligibility criteria**:** patients meeting the ATS criteria for 'refractory' asthma with evidence of ongoing eosinophilic inflammation (sputum differential cell count ≥3% or blood eosinophils ≥0.4×109/mL)
Setting	United Kingdom
Interventions	Ciclesonide 320 mg twice daily or placebo for 8 weeks in addition to their usual maintenance medication
Adherence reported yes/no	Yes
Primary outcomes	The change in sputum differential eosinophil count between randomisation and week 8
Secondary outcomes	ACQ score, AQLQ score, pre-bronchodilator FEV1, bronchial NO and alveolar NO at week 8.

Study reference	Holgate (Omalizumab) 2004
Study title	Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma
Study duration	6–10-week run-in period. 32 weeks
Trial registration:	Not documented
Study Population	Participants: Omalizumab, n=126; placebo, n=120 **Eligibility criteria:** patients aged 12–75 years; required 1000 mg/day fluticasone for symptom control (all patients were switched to inhaled fluticasone during the run-in period); demonstration of a positive skin prick test to aeroallergen/s, and had serum total IgE 30–700 IU/mL
Setting	Canada and European countries
Interventions	Omalizumab administered subcutaneously [minimum 0.016mg/kg/IgE (IU/mL) per 4 weeks; or matching placebo at intervals of 2 or 4 weeks
Adherence reported	No
Primary outcomes	The percentage reduction from baseline in fluticasone dose after 32 weeks' treatment
Secondary outcomes	Absolute reduction in fluticasone dose compared to baseline, asthma exacerbation episodes, use of rescue medication, asthma symptom score, peak expiratory flow (PEF) and post-bronchodilator spirometry, QoL.

Study reference	Holgate (Etanercept) 2011
Study title	Efficacy and safety of etanercept in moderate-to-severe asthma: a randomised, controlled trial
Study duration	12 weeks
Trial registration:	NCT00141791
Study Population	Participants: etanercept group, n=68; placebo group, n=64 Eligibility criteria: patients of the age 18–70 years, with moderate to severe persistent asthma{defined by the National Heart, Lung and Blood Institute (NHLBI)} for at least 1 year; demonstrated reversibility of at least 9% and (FEV1) 50% to 80% predicted after a SABA or 12 h after a LABA at screening or baseline; have a mean ACQ-5 score of ≥2; treated with high-dose ICS (≥1,000 µg/day beclomethasone–chlorofluorocarbons, 500 mg/day beclomethasone–hydrofluoroalkane, 500 mg/day fluticasone or 1,000 mg/day budesonide, or equivalent); and be receiving stable doses of their current medications for asthma >4 weeks prior to randomisation
Setting	United States
Interventions	Subcutaneous injection of either 25 mg ETN or placebo twice weekly
Adherence reported	No
Primary outcomes	Change in FEV1% predicted from baseline to week 12 (before bronchodilator administration)

Secondary outcomes	The change in PEFR, ACQ, asthma exacerbations at week from baseline to week 12

Study reference	Humbert (Omalizumab) 2005
Study title	Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE
Study duration	7-day screening period; 8-week run-in period. 28 weeks
Trial registration:	Not documented
Study Population	Participants: Omalizumab group, n=209; placebo group, n=210 Eligibility criteria: positive skin prick test to ≥1 aeroallergen; serum IgE: 30 to 700 IU/mL; severe persistent asthma requiring > 1000 BDP or equivalent and LABA treatment; FEV1 40% to 80%; FEV1 reversibility ≥ 12% post SABA; ≥ two exacerbations requiring OCS in previous 12 months or one severe exacerbation resulting in hospitalisation
Setting	France, New Zealand, Scotland, Canada, France, Germany, Spain, Italy, United Kingdom
Interventions	Subcutaneous omalizumab (0.016 mg/kg per IU/mL) (plus usual care or placebo
Adherence reported	Yes
Primary outcomes	The rate of clinically significant asthma exacerbations during the 28-week double-blind treatment phase
Secondary outcomes	The change in asthma symptoms, morning PEF, rescue medication uses and FEV1, Asthma-related QoL from baseline to week 28

Study reference	Humbert (Masitinib) 2009
Study title	Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics
Study duration	16 weeks
Trial registration:	NCT00842270
Study Population	Participants: masitinib 3 mg/kg/day (n = 12); masitinib 4.5 mg/kg/day (n = 11); masitinib 6 mg/kg/day (n = 10); all masitinib groups, (n = 33): placebo group, (n = 11) Eligibility criteria: Patients of the age 18–75 years with a diagnosis of asthma for≥3 years and severe uncontrolled disease for ≥1 year; stable disease with no exacerbation episode for at least one month before inclusion; postbronchodilator reversibility in FEV1 of ≥12%; to have experienced asthma symptoms more than once in 3 days for ≥3 months before screening despite continuous treatment with high-dose ICS (beclomethasone ≥1000mg or equivalent), LABA and daily oral corticosteroids (10–50 mg of equivalent prednisolone, with stable dosage for at least 3 months) and (iii) patients had to be non-smokers for at least 1 year with a prior tobacco consumption of <10 pack-years
Setting	France
Interventions	One of four masitinib groups for a 16-week treatment period: masitinib at 3, 4.5 or 6 mg/kg/day or placebo control
Adherence reported	No

Primary outcomes	The decrease in oral corticosteroid therapy (weaning extent) at week 16
Secondary outcomes	Asthma control/ improvement and asthma exacerbation rate at week 16

Study reference	Juergens (Eucalyptol) 2003
Study title	Anti-inflammatory activity of1.8 -cineol (eucalyptol) in bronchial asthma: a double-blind placebo-controlled trial
Study duration	2 months run in. 12 weeks
Trial registration:	Not documented
Study Population	Participants: 1.8 -cineol group, n=16; placebo group, n=16 Eligibility criteria**:** a reversibility of at least 15% in FEV1 10 min after inhalation of 200 mg fenoterol, and an airway resistance (RAW) below 0.6 kPa(l/s); Lung function criteria and values conformed to ATS guidelines
Setting	Germany
Interventions	1.8 -cineol 200 mg here times per day (at 8 a.m., 2 p.m., and 8 p.m.) or placebo capsules
Adherence reported	No
Primary outcomes	The change from the baseline to week 12 of oral steroid dosage
Secondary outcomes	The duration of dose reduction tolerated and stable lung function as determined by body plethysmography, stable clinical condition as measured by outpatient PEFR, symptom scores and bronchodilators use, and overall assessment of efficacy by the patient and the study physician

Study reference	Kaler (Pioglitazone) 2017
Study title	A randomized, placebo-controlled, double-blinded, crossover trial 2 of pioglitazone for severe asthma
Study duration	4-week run-in period. 44 weeks
Trial registration:	Not documented
Study Population	Participants: pioglitazone group, n=14; placebo group, n=12 Eligibility criteria: severe asthmatics, between 18 and 75 years of age, who were persistently symptomatic and required use of a rescue β2-agonist inhaler > 2x per week despite treatment with high-dose inhaled corticosteroids (e.g., equivalent to > 1,000mg daily of fluticasone propionate inhalation powder) or oral corticosteroids; documented history of reversible airflow obstruction, as defined by a positive response to an inhaled bronchodilator or a positive methacholine bronchial provocation challenge, as well as a left ventricular ejection fraction of > 50% by echocardiography
Setting	United States
Interventions	Pioglitazone 30mg daily or matching placebo (crossover trial)
Adherence reported	No
Primary outcomes	The between group change in AQLQ from baseline to 16 weeks
Secondary outcomes	The change in ACQ score, daily asthma symptom score, rescue inhaler utilization (number of puffs/day), asthma symptom-free days, nights with asthma symptoms, asthma exacerbations (mild

	and severe), pre- and post-bronchodilator FEV1, blood inflammatory cell counts (eosinophils, neutrophils, lymphocytes, monocytes and basophils), serum IgE levels, and FeNO from baseline to week 16

Study reference	Kanzow (Methotrexate) 1995
Study title	Short term effect of methotrexate in severe steroid-dependent asthma
Study duration	3-week run-in period. 16 weeks of treatment period and 8 weeks of run-out period
Trial registration:	Not documented
Study Population	Participants: methotrexate group, n=12, Placebo group, n=9 Eligibility criteria: age>30 years; diagnosis of asthma as per ATS criteria; continuous use of oral prednisolone or its equivalent for >1 year at a minimum dose of 15mg/day with at least one documented corticosteroid toxicity; high-dose ICS (beclomethasone/budesonide at least 800µg/day
Setting	Germany
Interventions	15mg methotrexate or identical placebo
Adherence reported	No
Outcomes	Reduction in prednisolone dose, PEFR, FEV1, symptom score, Nocturnal awakenings

Study reference	Kenyon (L-Arginine) 2011
Study title	L-Arginine supplementation and metabolism in asthma
Study duration	3 months
Trial registration:	NCT00280683
Study Population	Participants: L-arginine group, n=10; placebo group, n=10 Eligibility criteria**:** moderate to severe persistent asthma, were at least 18 years of age, not pregnant; patients did not have an acute exacerbation at the time of enrolment and were on the same asthma medications for at least one month
Setting	United States
Interventions	0.01 g/kg/day of L-arginine in divided doses for three months. Placebo tablets that match the L-arginine intervention tablets were given for three months
Adherence reported	No
Primary outcomes	Number of asthma exacerbations in three months
Secondary outcomes	L-arginine serum concentration (Time Frame: 90 days)

Study reference	Kerstjens (Tiotropium) 2011
Study title	Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial
Study duration	2-week run-in period. 24 weeks
Trial registration:	NCT00365560
Study Population	Participants: 107 patients randomised Eligibility criteria: patients of the age 18 to 75 years with at least a 5-year history of asthma and a current diagnosis of severe persistent asthma; They were persistent airflow obstruction and symptomatic with ACQ-5 score of ≥1.5; postbronchodilator FEV1 of ≤80% of predicted value and ≤70% of FVC 30 minutes after inhalation of 4x100µg of salbutamol at screening) despite therapy with a high-dose ICS (≥800 mg of budesonide or equivalent, see this article's Online Repository) and a LABA; non-smokers or not have smoked for a year and have a smoking history of <10 pack-years
Setting	Germany, Denmark and Netherlands
Interventions	Random sequence for 8 weeks in a crossover design (5 or 10 mg of tiotropium or matching placebo administered as 2 actuations once daily through the Respimat inhaler)
Adherence reported	No
Primary outcomes	The FEV1 response (within 3 hours post dosing) determined at the end of the 8-week treatment period

Secondary outcomes	The trough FEV1 and peak and trough FVC at the end of each 8–week treatment period, the area under the curve (AUC) of the first 3 hours of FEV1 (FEV1 AUC0-3h) and FVC (FVC AUC0-3h) and weekly means of pre dose morning and evening PEF and FEV1, asthma symptoms (5-point rating scale), use of rescue medication in the last 5 weeks of treatment, asthma symptom-free days, and AQLQ

Study reference	Kerstjens (Tiotropium) 2015
Study title	Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials
Study duration	4-week run-in period. 24 weeks
Trial registration:	NCT01172808 and NCT01172821
Study Population	Participants: tiotropium 5µg group, n=519; tiotropium 2·5µg group, n=520; salmeterol group, n=541; or placebo group, n=523 Eligibility criteria: male or female, aged between 18 and 75 years, and had been diagnosed with asthma before age 40 years and at least 3 months before enrolment; diagnosis of asthma confirmed at screening on the basis of bronchodilator reversibility, with an FEV1 increase of ≥12% and ≥200 mL 5–30 min after 400µg salbutamol; symptomatic (mean ACQ-7 score of ≥1·5) at screening and before randomisation, had to have a pre-bronchodilator FEV1 60–90% of predicted at screening, and had to show FEV1 variability at randomisation within plus or minus 30% of the screening value. stable treatment with medium-dose inhaled corticosteroids of 400–800µg budesonide or equivalent (alone or in fixed combination with a LABA or short-acting β2 agonist) for at least 4 weeks before screening. Patients were to have never smoked or been ex-smokers for more than 1 year, with a total of ≤10 pack-years
Setting	233 sites in 14 countries (Latvia, Poland, Romania, Russia, Brazil, China, Colombia, Germany, Guatemala, India, Japan, Mexico, Peru, and the USA)

Interventions	Once daily tiotropium 5µg or 2·5µg, twice-daily salmeterol 50µg, or placebo.
Adherence reported	No
Primary outcomes	The peak FEV1 response, measured within the first 3 h after evening dosing, and trough FEV1 response, measured at the end of the dosing interval (24 h after drug administration), 10 min before the next dose, both determined at the end of the 24-week treatment period. The improvement in ACQ-7 score of ≥0·5 or more at the end of week 24
Secondary outcomes	All determined at the end of the 24-week treatment period, included peak FVC, trough FVC, mean weekly pre-dose morning PEF response, and mean weekly pre-dose evening PEF response, AQLQ, and times to first severe asthma exacerbation and first asthma exacerbation (both during the 24-week treatment period)

Study reference	Kishiyama (IVIG) 1999
Study title	A Multicentre, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma
Study duration	2-month observation/run-in period. 7 months
Trial registration:	Not documented
Study Population	Participants: IVIG (2 gm/kg) group, n=16; IVIG (1 gm/kg) group, n=9; placebo group, n=15 Eligibility criteria: patients of the age 6 to 66 years with a previously diagnosis of asthma, defined by the ATS criteria; unable to decrease their steroid dosage to <0.1 mg/kg/day prednisone (or the equivalent) during the prior 3 months of optimizing therapy or failed to maintain peak flows of > 80% of predicted values on their current dose of prednisone
Setting	United States
Interventions	2 g IVIG/kg/month, 1 g IVIG/kg/month, or 2 g IV albumin (placebo)/kg/month.
Adherence reported	No
Primary outcomes	The mean daily prednisone-equivalent dose requirements determined during the observation month preceding initiation of treatment and compared to the month preceding the seventh infusion

Secondary outcomes	FEV1, frequency of emergency room visits or hospitalizations, and number of days absent from school or work

Study reference	Lanier (Omalizumab) 2003
Study title	Omalizumab is the effective in the long-term control of severe allergic asthma
Study duration	24 weeks
Trial registration:	Extension phase of Busse 2001
Study Population	Participants: omalizumab group, n= 245; placebo group, n=215 Eligibility criteria: male or female allergic asthmatics aged 12 to 75 years who were symptomatic despite treatment with ICSs; duration of asthma ≥1 year; positive immediate responses on skin prick testing to at least 1 common allergen, including Dermatophagoides farinae, Dermatophagoides pteronyssinus, cockroach (whole body), dog, or cat; total serum IgE ≥30 IU/mL to ≤700 IU/mL; FEV1 reversibility of ≥12% within 30 minutes after administration of albuterol (90-180 μg); baseline FEV1 ≥40% and ≤80% of predicted; and treatment with 420 to 840 μg/day of beclomethasone dipropionate (BDP) or its equivalent ICS for ≥3 months prior to randomization
Setting	United States and United Kingdom
Interventions	placebo or omalizumab subcutaneously every 2 or 4 weeks, depending on baseline IgE level and body weight
Adherence reported	No
Primary outcomes	The number of patients experiencing at least 1 asthma exacerbation

Secondary outcomes	FEV1

Study reference	Laviollette (Benralizumab) 2013
Study title	Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia
Study duration	14-day screening period. 84 days
Trial registration:	NCT00659659
Study Population	Participants: Cohort 1; benralizumab,1 mg/kg group, n= 8; placebo group, n = 5. Cohort 2: benralizumab, 100 mg group, n= ; benralizumab 200 mg group, n =5; placebo group, n =5 Eligibility criteria: patients of the age 18 to 65 years; documented diagnosis of asthma supported by at least 1 of the following criteria: (1) 12% or greater increase in FEV1 after inhalation of 400 mg of albuterol during screening, (2) history of ≥12% FEV1 reversibility within 1 year of randomization, or (3) history of 20% reduction in FEV1 in response to a provocative methacholine challenge (PC20) of less than 8 mg/mL within 1 year of randomization; sputum eosinophil counts of ≥2.5%, postbronchodilator FEV1 of ≥65%, prebronchodilator FEV1/FVC ratio of less than age-adjusted norms, and an asthma therapeutic regimen that was unchanged for 4 weeks before randomization and maintained from screening to the first follow-up airway mucosal/submucosal biopsy
Setting	3 United States and 4 Canadian medical centres.
Interventions	Intravenous infusion of 1 mg/kg benralizumab or placebo (2:1) on day 0 (cohort 1) or 100 or 200 mg of benralizumab or placebo (1:1:1) delivered in 4 subcutaneous injections on days 0, 28, and 56 (cohort 2).

Adherence reported	No
Primary outcomes	Safety and the effect of benralizumab on eosinophil counts in airway mucosal/submucosal biopsy specimens 28 days after completion of dosing
Secondary outcomes	Evaluate the pharmacokinetics (PK) of MEDI-563 in adults with atopic asthma and evaluate the immunogenicity (IM) of MEDI-563 in adults with atopic asthma. [Time Frame: Day 84 or 140]

Study reference	Li (Omalizumab) 2014
Study title	Omalizumab improves quality of life and asthma control in Chinese patients with moderate to severe asthma: a randomized phase III study
Study duration	6-week screening period. 24 weeks.
Trial registration:	NCT01202903
Study Population	Participants: omalizumab group, n=310; placebo group, n=299 Eligibility criteria: patients of the age 18-75 years, with confirmed diagnosis of moderate-to-severe persistent allergic asthma {inadequately controlled symptoms despite medium-to high-dose ICS+LABA (GINA step 4) therapy; positive reaction to at least 1 perennial aeroallergen and reported ≥2 or ≥3 exacerbation events in previous 12 or 24 months, respectively; FEV1 of 40%-80% of predicted normal with post-bronchodilator reversibility of ≥12% within 30 minutes and compliance with completion of PEF electronic diary during the run-in period
Setting	Centres in China
Interventions	Add-on omalizumab or add-on placebo by subcutaneous injections for 24 weeks
Adherence reported	No
Primary outcomes	The mean change from baseline in morning PEF (am PEF, L/min) measured using a PEF meter after 24 weeks of treatment

Secondary outcomes	FEV1 % predicted at weeks 16 and 24 weeks and ACQ, AQLQ, Global Evaluation of Treatment Effectiveness (GETE) responder analysis, scores at Weeks 16 and 24. The rate and seasonal effect of protocol-defined asthma exacerbations were assessed as exploratory outcomes

Study reference	Lock (Ciclosporin) 1996
Study title	Double-blind, placebo-controlled study of cyclosporin a as a corticosteroid-sparing agent in corticosteroid-dependent asthma
Study duration	4-week run-in period. 52 weeks
Trial registration:	Not documented
Study Population	Participants: cyclosporin group, n=19; placebo group, n=20 Eligibility criteria: corticosteroid-dependent asthmatic patients; documented variability of at least 20% in their FEV1 or PEFR, either spontaneously or following treatment with a bronchodilator (nebulized salbutamol 5mg)
Setting	United Kingdom
Interventions	Cyclosporin at a starting dose of 5mg/kg/d (ideal body weight) or identical placebo presented as capsules, for a period of 36 weeks
Adherence reported	No
Primary outcomes	Reduction in prednisolone dosage at 36 weeks
Secondary outcomes	FEV1/FVC, response to bronchodilator, diurnal variability of PEFR, or day/night symptom scores

Study reference	Lomia (Carbamazepine) 2006
Study title	Bronchial asthma as neurogenic paroxysmal inflammatory disease: A randomized trial with carbamazepine
Study duration	4-week run-in period. 13 weeks
Trial registration:	Not documented
Study Population	Participants: carbamazepine group, n= 37; placebo group, n=37 Eligibility criteria: asthma diagnosis for at least for 1 year, poorly controlled asthma due to various reasons, absence of long-term remissions of asthma (lasting more than 1 month), and if pulmonary function testing demonstrated at least 12% acute response in FEV1 to beta-agonist inhalation
Setting	Georgia
Interventions	100 mg capsules of carbamazepine) or placebo for 13 weeks
Adherence reported	No
Primary outcomes	Efficacy of carbamazepine was evaluated by disappearance of any asthmatic syndrome, and normalization of PEF, FEV1
Secondary outcomes	The daytime scores of asthma, number of night-time awakening per week due to asthma symptoms and also by discontinuation of any other anti-asthmatic therapy except carbamazepine

Study reference	Marin (Nedocromil sodium) 1996
Study title	Effects of nedocromil sodium in steroid resistant asthma: a randomized controlled trial
Study duration	2-week observation period. 2 years
Trial registration:	Not documented
Study Population	Participants: Nedocromil sodium group, n=13, placebo group, n=13 Eligibility criteria: non-smoking adults (>18 years of age) with moderate or severe asthma; inadequately controlled by means of inhaled or orally administered corticoids; basal FEV1 <70% of the predicted
Setting	Spain
Interventions	Nedocromil sodium or placebo by means of a manual nebulizer for 3 months
Adherence reported	Yes
Primary outcomes	Morning PEF (L/min) and the daily use of inhaled salbutamol
Secondary outcomes	FEV~ value, variability of the PEF, value of the questionnaire for quality of life, intake of prednisolone, and number of asthma attacks that occurred during the treatment period. The changes found in FEV 1 between the groups during each visit and the mean morning PEF values, together with the use of salbutamol during the week before each visit in the treatment and washout periods, were compared with their baseline values

Study reference	Morjaria (Etanercept) 2008
Study title	The role of a soluble TNFα receptor fusion protein (etanercept) in corticosteroid 'refractory' asthma: a double blind, randomised, placebo-controlled trial
Study duration	2-week run-in period. 16 weeks
Trial registration:	Not documented
Study Population	Participants: etanercept group, n=13; placebo group, n=13 Eligibility criteria: severe 'refractory' asthma as per GINA guidelines {current treatment with oral prednisolone (2–30 mg/day) and/or high dose ICS (>2000µg/day beclomethasone equivalent) and LABA}; variable airflow obstruction and/or BHR confirmed by an increase in FEV1 by at least 12% after inhalation of 400 µg of salbutamol delivered by a metered dose inhaler and spacer, the concentration of methacholine required to cause a 20% (PC20) reduction in FEV1 of <8 mg/ml
Setting	United Kingdom
Interventions	50 mg of etanercept or matched placebo by subcutaneous injections once a week for 12 weeks
Adherence reported	Yes
Primary outcomes	The differences in change of the mean AQLQ score from baseline (visit 0) and the end of treatment (week 12) and change in mean ACQ scores from baseline and the last two treatment visits (week 12 and week 14)

Secondary outcomes	The differences from baseline to visit 12 for BHR, and to the last two treatment visits for predicted FEV1, FEV1/FVC, morning, evening and average daily PEF, and diurnal variation in PEF (calculated by the difference in the evening and morning PEF values)

Study reference	Nair (SCH 527123) 2012
Study title	Safety and efficacy of a CXCR2 antagonist in patients with severe asthma and sputum neutrophils: a randomized, placebo-controlled clinical trial
Study duration	2-week run-in period. 4 weeks
Trial registration:	Not documented
Study Population	Participants: SCH527123 group, n=22; placebo group, n=12 Eligibility criteria: patients of the age 18 and 70 years with severe asthma, meeting the National Heart Lung Blood Institute Severe Asthma Programme criteria; asthma diagnosis: ≥12% and 200 mL improvement in FEV1 after inhaling salbutamol or by a methacholine PC20 of < 8 mg/mL within the past 5 years; treatment with inhaled beclomethasone or equivalent in a dose of > 1000µg daily; sputum neutrophil differentials of > 40% at the screening visit, a total cell count of < 10 million cells/g of sputum selected from saliva and had negative standard cultures for bacteria: non-smokers for at least a year, had < 20 pack-years of smoking, were stable for the past 4 weeks and had been on stable treatment under the care of a specialist for at least 3 months
Setting	8 academic centres in Canada, Germany, Greece, France, Italy and the United Kingdom
Interventions	SCH527123 30 mg ingested once daily or a matching placebo for 4 weeks
Adherence reported	No

Primary outcomes	Safety as defined by the proportion of subjects in each treatment group who maintain a peripheral neutrophil count 1500/lL during the 4-week treatment period
Secondary outcomes	The change in ACQ score, minor and major exacerbations, PEF and sputum neutrophil activation markers in the 4-week treatment period

Study reference	Nair (Mepolizumab) 2009
Study title	Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia
Study duration	6-week run-in period. 26 weeks
Trial registration:	NCT00292877
Study Population	Participants: mepolizumab group, n=9; placebo group, n=11 Eligibility criteria: patients of the age 18-70 years, who have been found to require a minimum dose of prednisone treatment (in addition to high-dose inhaled steroid treatment) to prevent frequent exacerbations associated with induced sputum eosinophilia; on the same doses of corticosteroids for a least one-month
Setting	Hamilton, Ontario, Canada
Interventions	Mepolizumab 750mg or an identical placebo (normal saline diluent) was given intravenously over a 30-minute period at weeks 2, 6, 10, 14, and 18

Adherence reported	No
Primary outcomes	The proportion of patients with exacerbations in each study group and the mean reduction in the dose of prednisone as a percentage of the maximum possible reduction
Secondary outcomes	The reduction in the number of eosinophils in sputum and blood in phase 1; the time to an exacerbation, a reduction in the number of sputum and blood eosinophils, and changes in FEV1 and symptom scores in phase 2; and a reduction in the number of sputum and blood eosinophils and changes in FEV1 and symptoms in phase 3

Study reference	Nair (Benralizumab) 2017
Study title	Oral glucocorticoid–sparing effect of benralizumab in severe asthma
Study duration	8-week run-in period. 28 weeks
Trial registration:	NCT02075255
Study Population	Participants: benralizumab, 4-weekly group, n=72; benralizumab 8-weekly group, n =73; placebo group, n=75 Eligibility criteria: female and male aged from 18 to 75 years; physician-diagnosed asthma requiring treatment with medium- to high-dose ICS (total daily dose equivalent to >250µg fluticasone dry powder formulation) and LABA for ≥12 months prior to enrolment; documented treatment with high-dose inhaled glucocorticoid total daily dose equivalent to >500µg fluticasone dry powder formulation) and LABA for ≥ 6 months prior to enrolment; peripheral blood eosinophil count of ≥150 cells/µl; chronic oral glucocorticoid therapy for ≥6 continuous months directly preceding enrolment(patients must have been receiving doses equivalent to 7.5–40 mg/d of prednisolone/prednisone at visit 1 and must have been on a stable dose for ≥2 weeks before randomization); evidence of asthma as documented by: (Airway reversibility (FEV1 ≥12% and 200 mL) demonstrated at visit 1, visit 2, or visit 3 (week –10, –8, or –6) using the Maximum Post-bronchodilator Procedure, or documented reversibility in the previous 24 months prior to enrolment, or Airway hyper-responsiveness (provocative concentration of methacholine causing a 20% drop in FEV1 methacholine concentration ≤8 mg/ml) documented in the previous 12 months prior to planned date of randomization, or Airflow variability in clinic FEV1 ≥20% between two consecutive clinic visits

	documented in the 12 months prior to the planned date of randomization (FEV1 recorded during an exacerbation were considered for this criterion); At least one documented asthma exacerbation in the 12 months prior to the date informed consent was obtained.
Setting	Argentina, Bulgaria, Canada, Chile, France, Germany, South Korea, Poland, Spain, Turkey, Ukraine, United States.
Interventions	Subcutaneous injections of benralizumab at a dose of 30 mg every 4 weeks, benralizumab at a dose of 30 mg administered every 4 weeks for the first three doses and then every 8 weeks (with placebo administered at the 4-week interim visits; hereafter referred to as the group that received benralizumab every 8 weeks), or placebo administered every 4 weeks
Adherence reported	Yes
Primary outcomes	The percentage reduction in the oral glucocorticoid dose from baseline (randomization at week 0) to the final dose at the end of the maintenance phase (week 28) while asthma control was maintained
Secondary outcomes	The percentages of patients who had a reduction in the average daily oral glucocorticoid dose of 25% or more, of 50% or more, or of 100% (discontinuation of oral glucocorticoid therapy) from baseline to end of the maintenance phase and the percentage of patients with an average final oral glucocorticoid dose of 5.0 mg or less per day while asthma control was maintained; the annual asthma exacerbation rate, the time to the first asthma exacerbation, the percentage of patients with at least one asthma exacerbation (including exacerbations associated with emergency department

	visits or hospitalization), the pre-bronchodilator FEV1, ACQ-6 score, and the AQLQ score

Study reference	Nizankowska (Ciclosporin) 1995
Study title	Treatment of steroid-dependent bronchial asthma with cyclosporin
Study duration	12-week baseline period. 42 weeks
Trial registration:	Not documented
Study Population	Participants: Cyclosporin group, n=34; placebo group, n=17 **Eligibility criteria:** non-smoking adults aged 25–57 years; severe chronic asthma; required long-term oral steroid treatment at a minimum dose of 5–35 mg daily, in addition to standard therapy consisting of theophylline, inhaled beclomethasone and β-mimetics; Airflow variability of ≥15% increase in FEV1 or in PEF following 200 µg fenoterol inhalation
Setting	Poland
Interventions	Cyclosporin or placebo for 12 weeks
Adherence reported	No
Primary outcomes	Outcomes: asthma symptoms score, (daily peak expiratory flow PEF and bi-weekly FVC, FEV1 and maximal mid- expiratory flow (MEF50), biochemical profile and blood cyclosporin
Secondary outcomes	Not specified

Study reference	Ogirala (IM triamcinolone) 1995
Study title	Single, high-dose intramuscular triamcinolone acetonide versus weekly oral methotrexate in life-threatening asthma: a double-blind study
Study duration	2-month run in. 5 months
Trial registration:	Not documented
Study Population	Participants: 360-mg dose of triamcinolone 360mg dose, n=6; Placebo triamcinolone group, n=7; control group, n = 6 Eligibility criteria: patients of either sex between the ages of 21 and 70 years, with a diagnosis of asthma as per ATS criteria; on chronic steroid therapy (at least 5 mg of prednisone or its equivalent daily) during the year prior to entry into the study; a history of life-threatening asthma attacks (requiring mechanical ventilation or treatment in the intensive care unit) at least once in the preceding 4 years
Setting	United states
Interventions	Group 1: a single 360-mg dose of triamcinolone acetonide intramuscularly, followed by placebo methotrexate tablets taken orally each week for 6 months Group 2: placebo (normal saline) triamcinolone injection at entry, followed by oral methotrexate at a dose of 7.5mg the first week, followed by 15 mg every week for 6 months Group3: control group, receiving a placebo triamcinolone injection on the first day, followed by placebo-methotrexate tablets each week for the ensuing 6 months

Adherence reported	No
Outcomes assessed	Outcomes: FEV1, PEFR, PC20

Study reference	Oh (MEDI528) 2013
Study title	A randomized, controlled trial to evaluate the effect of an anti-interleukin-9 monoclonal antibody in adults with uncontrolled asthma
Study duration	4-week screening period, a 13-week steroid stable treatment period, an 11-week steroid reduction treatment period, and a 22-week follow-up period
Trial registration:	NCT00968669
Study Population	Participants: MEDI-528 30mg group, n=80; MEDI-528 100mg group, n=80, or MEDI-528 300 mg group, n=80; placebo group, n=80 Eligibility criteria: patients of the age 18–65 years with BMI of 18–35 kg/m2 and a clinical diagnosis of asthma, confirmed by pre-bronchodilator FEV1 of ≥ 40% predicted and post-bronchodilator FEV1 reversibility ≥ 12% and ≥ 200 mL; poor asthma symptom control (ACQ-6 score of ≥ 1.5; daytime symptoms on ≥ 2 days/week, night-time awakening ≥ 1 night/week, rescue medication use on ≥ 2 days/week); ≥ 1 asthma exacerbation in the past year; medium to high-dose ICS or were eligible to take them based on Expert Panel Report 3 guidelines, and were started on medium to high-dose ICS at the start of the run-in phase of the study
Setting	53 sites in North America, Central America, South America, and Asia
Interventions	Placebo or one of three doses of MEDI-528 (30, 100, or 300 mg) subcutaneously every 2 weeks for 24 weeks (13 doses)
Adherence reported	No

Primary outcomes	The change from baseline in mean ACQ-6 score at week 13 among individual MEDI-528 treatment groups and placebo
Secondary outcomes	The change from baseline in mean ACQ-6 score at week 25, asthma exacerbation rates (week 25), pre-bronchodilator FEV1 (weeks 13 and 25), AQLQ scores; weeks 12 and 25), and the safety of MEDI-528 throughout the study period

Study reference	Ohta (Omalizumab) 2009
Study title	Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma
Study duration	2-week pre-treatment period, 16-week treatment period and 12-week follow up
Trial registration:	Not documented
Study Population	Participants: omalizumab group, n=158; placebo group, n=169 Eligibility criteria: patients (aged 20–75 years) with moderate-to-severe asthma according to the GINA guidelines; treated with beclomethasone dipropionate chlorofluorocarbon (CFC)-containing metered-dose inhaler at 800 mg/day (or equivalent), and one or more of the following additional controller medications recommended as step 3 and step 4 treatments LABA (sustained-release theophylline, leukotriene receptor antagonist (LTRA), oral corticosteroid); positive skin test or in vitro reactivity to a perennial aeroallergen; serum total IgE of 30–700 IU/mL; insufficient asthma control, (asthma symptoms interfere with night-time sleep one day/week or asthma symptoms restrict daily activities or rescue medication/SABA needed one day/week or PEF diurnal variation 20% on one day/week or FEV1 or mean PEF value in the range of 40–80% of the predicted normal value
Setting	Japan
Interventions	Omalizumab subcutaneous injection every two or four weeks according to the patient's pre-treatment bodyweight and baseline

	IgE levels, using a dosing table to provide a dose of at least 0.016 mg/kg per IU/mL of IgE or placebo
Adherence reported	No
Primary outcomes	The change from baseline in morning PEF (L/min), as recorded on diary cards at 16 weeks
Secondary outcomes	The change from baseline in FEV1, asthma symptom score, daily activity score, sleep score and rescue medication use, clinically significant asthma exacerbations at week 16

Study reference	Ortega (Mepolizumab) 2014
Study title	Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma
Study duration	1-6 weeks run-in period, 32-week treatment intervention and 8-week follow-up
Trial registration:	NCT01691521
Study Population	Participants: mepolizumab 75 mg group, n=191; mepolizumab 100 mg group, n=194; placebo group, n= 191 Eligibility criteria: Blood eosinophils ≥ 150 cells/µL at screening or ≥ 300 cells/µL in previous 12 months; ≥ 2 exacerbations in previous 12 months; FEV1 < 80%; maintenance treatment with high-dose ICS for ≥ 12 months; plus additional controller for ≥ 3 months; ± maintenance OCS
Setting	Baltimore, Middlesex, Ghent, Vancouver, Parma, Marseille and Paris
Interventions	Mepolizumab in a 75 mg intravenous dose versus mepolizumab in a 100 mg subcutaneous dose versus placebo every 4 weeks for 32 weeks
Adherence reported	No
Primary outcomes	Number of annualized frequencies of clinically significant exacerbations
Secondary outcomes	Number of clinically significant exacerbations requiring hospitalisation (including intubation and admittance to an intensive care unit) or ED visits per year Mean change from baseline in clinic pre-bronchodilator FEV1 at

	week 32 Mean change from baseline in the SGRQ total score at week 32

Study reference	Park (Benralizumab) 2016
Study title	A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan
Study duration	52 weeks
Trial registration:	NCT01238861
Study Population	Participants: benralizumab 2 mg group, n=26; benralizumab 20 mg group, n=25; benralizumab 100 mg group, n=26; placebo group, n=26 Eligibility criteria: moderate/severe (based on ICS dose (medium/high); post-bronchodilator FEV1 reversibility ≥ 12% and ≥ 200 mL, or a positive response to methacholine challenge (PC20 ≤ 8 mg/mL); 2-6 exacerbations in the previous 12 months; ACQ-6 score ≥ 1.5 at least twice during screening; morning pre-bronchodilator FEV1 40%-90%; maintenance treatment with medium- to high-dose ICS in combination with LABA for ≥ 12 months
Setting	32 sites in South Korea and Japan
Interventions	Subcutaneous doses given at weeks 1, 4, 8, 16, 24, 32, 40. Benralizumab 2 mg, 20 mg or 100 mg subcutaneously
Adherence reported	No
Primary outcomes	Asthma exacerbation rate at week 52
Secondary outcomes	FEV1, PEFR, ACQ-6, FeNO, Exploratory endpoints included blood eosinophil counts.

Study reference	Pavord (Bronchial thermoplasty) 2007
Study title	Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma
Study duration	2-week run-in period. 52 weeks
Trial registration:	NCT 00214539
Study Population	Participants: Bronchial thermoplasty group, n= 15; control group, n= 17 Eligibility criteria: patients with asthma aged 18 to 65 years; requirement of high-dose ICS (≥750 mg fluticasone propionate per day or equivalent) and LABA (at least 100 mg salmeterol per day or equivalent), with or without oral prednisone (<30 mg/d), leukotriene modifiers, or theophylline; prebronchodilator FEV1 > 50% of predicted; demonstrable airway hyperresponsiveness by challenge with methacholine or reversible bronchoconstriction during prior 12 months as demonstrated by an increase in FEV1 of at least 12% 30 minutes after four puffs of a SABA; uncontrolled symptoms despite taking maintenance medication (demonstrated by the use of rescue medication on at least 8 of the 14 days before enrolment, or daytime symptoms on at least 10 of the 14 days before enrolment); and abstinence from smoking for ≥1 year and past smoking history of <10 pack-years
Setting	8 investigational sites in three countries; Canada, United Kingdom and Brazil

Interventions	Bronchial thermoplasty in addition to ICS/LABA or ICS plus LABA. Bronchial thermoplasty group patients underwent three procedures at least 3 weeks apart
Adherence reported	Yes
Primary outcomes	The safety of BT was assessed by monitoring adverse events and PEF between weeks 6 to 22
Secondary outcomes	The change in OCS and ICS, use of rescue medication, morning and evening PEF, FEV1, PC20 (provocative concentration causing a 20% fall in FEV1), asthma symptom score, symptom-free days, or AQLQ and ACQ scores PEF between weeks 6 to 22

Study reference	Pavord (Mepolizumab) 2012
Study title	Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial
Study duration	52-week
Trial registration:	NCT01000506
Study Population	Participants: mepolizumab 750 mg group, n=156; mepolizumab 250 mg group, n=152; mepolizumab 75 mg group, n=154; placebo group, n=159 Eligibility criteria: ≥ 3% sputum eosinophils or blood eosinophil ≥ 300 cells/µL; ≥ 2 exacerbations in previous 12 months; maintenance treatment with high-dose ICS (i.e. ≥ 880µg/d FP or equivalent daily); + additional controller; ± maintenance OCS ;patients were aged 12–74 years and had a clinical diagnosis of asthma supported by one or more other characteristics: variability in diurnal PEF of more than 20% for at least 3 days during the 2-week run-in period; improvement in FEV1 of more than 12% and 200 mL after 200µg inhaled salbutamol at visit one or two, or in the 12 months before study entry; a variability in FEV1 of greater than 20% between two consecutive clinic visits in 12 months; or a provocative concentration of inhaled methacholine needed to reduce FEV1 by 20% (PC20) of 8 mg/mL or less documented in the 12 months before study entry
Setting	81 centres in 13 countries; Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russia, Ukraine, the United Kingdom and the United States

Interventions	13 total intravenous infusions of mepolizumab (750 mg), mepolizumab (250 mg), mepolizumab (75 mg) or placebo given every 4 weeks
Adherence reported	No
Primary outcomes	The rate of clinically significant asthma exacerbations. Exacerbation events occurring in the 52 weeks between completion of the first treatment visit and 4 weeks after the final treatment visit were included in the analysis
Secondary outcomes	The rate of exacerbations requiring admission, visits to the emergency department, blood and sputum eosinophil counts, mean change from baseline in clinic pre-bronchodilator FEV1, ACQ, AQLQ over the 52-week treatment period, time to first clinically significant exacerbation requiring oral or systemic corticosteroids, hospitalisation, and/or ED visits, frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits

Study reference	Piper (Tralokinumab) 2013
Study title	A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma
Study duration	2-week run-in period. 24 weeks
Trial registration:	NCT01402986
Study Population	Participants: tralokinumab 150mg group, n=47; tralokinumab 300mggrop, n=51; tralokinumab 600mg group, n=48; placebo group, n=48 Eligibility criteria**:** patients age, 18–65 years; BMI of 18–40 kg/m2 physician-diagnosed, moderate-to-severe uncontrolled asthma; reversible airflow obstruction (post-bronchodilator FEV1 reversibility ≥12% and ≥200 mL either documented within the previous year or at screening); pre-bronchodilator FEV1 of 40% predicted value; ACQ-6 score of ≥1.5 at screening and randomisation, and one or more asthma exacerbations that required medical intervention in the past year
Setting	United Kingdom and United states
Interventions	Tralokinumab 150, 300 or 600 mg or placebo. Treatment was administered every 2 weeks by subcutaneous injection
Adherence reported	Yes
Primary outcomes	The change from baseline to week 13 in mean ACQ-6 score

Secondary outcomes	Time to asthma control, change from baseline in FEV1 and peak PEF (at study visit and at home), time to first asthma exacerbation, asthma exacerbation rate, requirement for concomitant asthma rescue medications, daily asthma symptoms scores, AQLQ, pre-bronchodilator FEV1, FVC and PEF. Patient-reported outcomes (PROs) included a four-item

Study reference	Robinson (Montelukast) 2001
Study title	Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial
Study duration	4 weeks
Trial registration:	Not documented
Study Population	Participants: 100 patients randomised, cross over trial Eligibility criteria: Any patient with a physician diagnosis of asthma in whom the recruiting consultant physician felt a trial of Montelukast was indicated for continued asthma symptoms despite other anti-asthma
Setting	United Kingdom
Interventions	Montelukast sodium or matched placebo capsules for four weeks
Adherence reported	No
Outcomes assessed	PEF, FEV1

Study reference	Rubin (Omalizumab) 2012
Study title	Effect of Omalizumab as Add-On Therapy on Asthma-Related Quality of Life in Severe Allergic Asthma: A Brazilian Study (QUALITX)
Study duration	20 weeks
Trial registration:	Not documented
Study Population	Participants: Omalizumab group, n=78; control group, n=38 Eligibility criteria**:** patients of the age 12 and 75 years; severe persistent asthma as per GINA guidelines; uncontrolled despite treatment with, at least, ICS (500 µg/day of fluticasone equivalent) and LABA; 20 and 150 kg body weight; serum total IgE levels between 30 and 700 IU/mL; positive skin prick test (diameter of wheal 3 mm) for at least one perennial aeroallergen
Setting	Brazil
Interventions	Omalizumab+ LABA + ICS or the control group (LABA + ICS). Omalizumab 150–375 mg was administered subcutaneously every 2 or 4 weeks
Adherence reported	No
Primary outcomes	The mean change from baseline in overall AQLQ score in omalizumab-treated patients compared with the control group mean change at week 12 and at week 20
Secondary outcomes	Rescue medication use, incidence of asthma exacerbations, perception of treatment efficacy among patients, mean change from baseline in AQLQ score, and >1.5-point increase in overall

	AQLQ score percentage of patients with a >1.5-point increase from baseline in the overall AQLQ; FEV1, FVC, Global Evaluation of Treatment Effectiveness

Study reference	Salmun (IVIG) 1999
Study title	Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: A double-blind, placebo controlled randomized trial
Study duration	3 months
Trial registration:	Not documented
Study Population	Participants: Immune Globulin Intravenous 5% group, n=16, placebo group, n=12 Eligibility criteria: Age 5 to 35 years with a clinical diagnosis of asthma per ATS criteria; steroid dependent asthma (patients who required oral steroid on a daily or alternate day basis for at least 6 months before study entry or patients who required at least 30 days of oral steroids per year despite chronic use of inhaled steroids)
Setting	Massachusetts, Turkey, Austria
Interventions	Iveegam Immune Globulin Intravenous 5%, and 5% albumin was the placebo
Adherence reported	No
Primary outcomes	Comparison of dosage of oral steroids consumed at baseline (first 3 months of the study) and a during the treatment phase (the last 3months of the study)
Secondary outcomes	Comparison of dosage other medication use, parameters of clinical symptomatology, and pulmonary function tests at baseline(first 3

	months of the study) and a during the treatment phase (the last 3months of the study)

Study reference	Sano (Sodium cromoglycate) 2006
Study title	Effects of nebulized sodium cromoglycate on adult patients with severe 'refractory' asthma
Study duration	2-week observation period. 10 weeks
Trial registration:	Not documented
Study Population	Participants: sodium cromoglycate group, n =114, placebo group, n =114 Eligibility criteria: Patients of the age ≥20; severe persistent asthma; Step 4 therapy according to the Classification for Asthma Severity in the Asthma Prevention and Management Guidelines 20001 in Japan; ICS regiment : 4800 mg/day of inhaled beclomethasone dipropionate (BDP-CFC), 4400 mg/day of inhaled fluticasone propionate (FP-DPI), or 4400 mg/day of inhaled budesonide (BUD-DPI); mean morning PEF during the observation period <80% of normal predicted value, or diurnal variation in PEF during the observation period >20% were evaluated at least 2 days/each week; asthmatic symptoms (wheezing, dyspnoea, or slight asthmatic attack) were reported at least 2 times/week
Setting	30 medical centres in Japan
Interventions	Sodium cromoglycate or isotonic saline was used as placebo
Adherence reported	No
Primary outcomes	The percentage change from baseline at the end of the treatment in morning PEF at 2, 4, 6, 8 and 10 weeks

Secondary outcomes	The change in FVC, FEV1, PEF, asthmatic symptom score, QOL at baseline, 4, 8 and 10 weeks

Study reference	Bosquet (Omalizumab) 2011
Study title	Persistency of response to Omalizumab therapy in severe allergic (IgE-mediated) asthma
Study duration	8-week run-in period. 32 weeks
Trial registration:	Not documented
Study Population	Participants: Omalizumab group, n=272, Optimised asthma therapy (OAT) group, n=128 Eligibility criteria: patients of the aged 12-75 years, with severe allergic asthma; ≥2 severe asthma exacerbations (requiring treatment with systemic corticosteroid s) while receiving ≥800µg beclomethasone dipropionate or equivalent plus LABA during the 3 years prior to screening, with ≥1 severe exacerbation within the previous year; body weight of 20-150kg and baseline serum IgE level of 30-700IU/ml: positive skin prick or radio-allergosobernt test to at least one perennial allergen; ≥12% reversibility in FEV1 within taking 2-4x100µg salbutamol; FEV1 between 40% and 80% of predicted
Setting	106 centres in 14 countries; Belgium, Canada, Denmark, Germany, Hungary, Israel, Italy, Norway, Poland, Spain, Sweden, turkey, United Kingdom and Switzerland
Interventions	Optimised asthma therapy (OAT) or optimised asthma therapy and omalizumab
Adherence reported	No

Primary outcomes	The persistency rate of response in patients receiving omalizumab at weeks 16 and 32
Secondary outcomes	Persistency rates of non-response in patients receiving omalizumab at weeks 16 and 32; persistency rates of response/nonresponse in patients receiving OAT alone; patients' GETE at weeks 16 and 32; change from baseline in FEV1 and %-predicted at weeks 16 and 32; clinically significant asthma exacerbations over the 32-week treatment period; severe exacerbations over the 32-week treatment period ; hospitalizations and total emergency room visits because of asthma exacerbation over the 32-week treatment period; change from baseline ACQ overall score which was assessed at weeks 16 and 32; change from baseline at week 32 in the number of night in the previous 2 weeks with an awakening requiring rescue medication

Study reference	Simpson (Clarithromycin) 2008
Study title	Clarithromycin targets neutrophilic airway inflammation in 'refractory' asthma
Study duration	12-week run-in period. 8 weeks treatment period
Trial registration:	No. 12605000318684
Study Population	Participants: Clarithromycin group, n=23; placebo group, n=23 Eligibility criteria: Non-smoking adults with symptomatic 'refractory' asthma according to GINA guidelines, with demonstrated airway hyperresponsiveness to hypertonic saline
Setting	Australia
Interventions	Oral clarithromycin 500 mg twice daily or placebo duration of treatment
Adherence reported yes/no	No
Primary outcomes	IL-8 levels in sputum supernatant after 8 weeks of treatment
Secondary outcomes	The sputum neutrophil numbers, neutrophil elastase and matrix metalloproteinase (MMP)-9 levels, FEV1% predicted, dose–response slope to hypertonic saline, symptom severity, asthma control score, and asthma quality-of-life questionnaire score

Study reference	Smith (Isoflavane) 2015
Study title	Effect of a Soy Isoflavone Supplement on Lung Function and Clinical Outcomes in Patients with Poorly Controlled Asthma A Randomized Clinical Trial
Study duration	6 months
Trial registration:	NCT01052116
Study Population	Participants: Isoflavane group, n=193; placebo group, n=193 Eligibility criteria: age ≥12; physician diagnosed asthma; pre-bronchodilator FEV1 ≥50% predicted; at least 12% increase in FEV1 15-30 minutes after inhaling 2-4 puffs of albuterol or positive methacholine challenge (20% fall in FEV1 at less than 8 mg/mL); prescribed daily controller asthma medication; non-smokers for ≥6months or longer with <10 pack-years smoking history; poor asthma control (at least one of the following: ACQ score of ≥1.5; use of beta-agonist for asthma symptoms two or more times per week; nocturnal awakening with asthma symptoms more than once per week); two or more episodes of asthma symptoms in the past 12 months with each requiring at least one of the following: emergency department visit, unscheduled physician visit, prednisone course, hospitalization
Setting	United States
Interventions	Soy isoflavone supplement or a matching placebo twice daily for 6 months
Adherence reported	No

Primary outcomes	The mean changes in prebronchodilator FEV1 over 24 weeks
Secondary outcomes	ACT score, the Asthma Symptoms Utility Index, AQLQ, PEF, symptom-free days (defined as days with no asthma episodes reported on diary card); and rates of episodes of poor asthma control

Study reference	Soler (Omalizumab) 2001
Study title	The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics
Study duration	4–6-week run-in period
Trial registration:	Not documented
Study Population	Participants: Omalizumab group, n=274; placebo group, n= 272 Eligibility criteria: age, 12-75years; diagnosis of asthma of at ≥1 yr. duration who met the standard criteria of ATS and the following additional criteria: a positive skin-prick test to at least one of the allergens Dermatophagoides farinae, D. pteronyssinus, dog or cat; serum total IgE level ≥30 and ≤700 International Units (IU)/mL and body weight ≤150 kg to allow optimal dosing of omalizumab; baseline forced expiratory volume in one second (FEV1) off bronchodilators ≥40% and ≤80% of predicted increasing by ≥12% within 30 min of taking inhaled salbutamol; a mean total daily symptom score of ≥3.0 (maximum 9) during the 14 days prior to randomization; treatment with inhaled corticosteroids in doses equivalent to 500–1,200 mg of beclomethasone dipropionate (BDP) per day for ≥3 months prior to randomization and use of b2-adrenoceptor agonists on an as-needed or regular basis; stable asthma, with no significant change in regular medication and no acute exacerbation requiring additional corticosteroid treatment for≥1 month prior to the screening visit
Setting	United States, Germany, United Kingdom and South Africa
Interventions	Omalizumab or placebo subcutaneously for 7 months every 4 weeks

Adherence reported	No
Primary outcomes	The number of asthma exacerbations experienced per patient during the stable-steroid phase (first 16 weeks of the study) and the steroid-reduction phase (the last 12 weeks of the study)
Secondary outcomes	The number of patients experiencing at least one asthma exacerbation during both the stable-steroid and the steroid-reduction phases, per cent reduction in the BDP dose at the end of the steroid-reduction phase as a continuous variable and by category, salbutamol rescue use, asthma symptom scores, morning PEF and FEV1 % predicted

Study reference	Tamaoki (Th2 inhibitor IL5/IL4) 2000
Study title	Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid dependent asthma: a double-blind randomised study
Study duration	2-week run-in. 8-week treatment period
Trial registration:	Not documented
Study Population	Participants: suplatast tosilate group, n= 43; placebo group, n= 42 Eligibility criteria: age ≥21 years, who had been taking 1500 g or more inhaled beclomethasone daily for at least 6 weeks before the study; asthma diagnosis as per the ATS guidelines; FEV1 predicted of at least 60% and a documented FEV1 reversibility of at least 15% of compared with baseline 15 min after inhalation of the 2-agonist procaterol (20g)
Setting	Japan
Interventions	Suplatast tosilate (100 mg per capsule three capsules daily) or placebo (identical in taste and appearance to suplatast tosilate)
Adherence reported	Yes
Outcomes assessed	PEFR, FEV1 and asthma symptoms scores at 4 and 8 weeks

Study reference	Vignola (Omalizumab) 2004
Study title	Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR
Study duration	4-week run-in. 28 weeks
Trial registration:	Not documented
Study Population	Participants: Omalizumab group, n =209; placebo group, n =196 Eligibility criteria: age 12–75 years; history of allergic asthma for at least 1 year with ≥ 12% increase in FEV1 after 400µg salbutamol; IgE level from ≥30 to ≤1300 IU/ml and a positive skin-prick test to at least one indoor allergen: moderate-to-severe persistent allergic rhinitis symptoms for ≥2 years was also necessary for inclusion: treated with ≥400 µg/day of ICS and had a history of ≥ 2 unscheduled medical visits for their asthma during the past year or ≥3 in the past 2 years: AQLQ score of >64/192; RQLQ>56/168 Rhinitis Quality of Life Questionnaire
Setting	United Kingdom, France, Canada, France and Italy
Interventions	Placebo or omalizumab administered every 2 or 4 weeks
Adherence reported	No
Primary outcomes	The incidence of asthma exacerbations during the 28-week treatment period and the proportion of patients with improvement in both asthma and rhinitis QoL scores

Secondary outcomes	Rescue-medication use, separate AQLQ and RQLQ evaluations, Wasserfallen asthma and rhinitis clinical symptom scores, patient and investigator global evaluations of treatment effectiveness, pulmonary function tests [FEV1, forced vital capacity (FVC), morning peak expiratory flow (PEF)] and ICS use

Study reference	Virchow (Zafirlukast) 2000
Study title	Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids
Study duration	2-week pre-randomisation phase. 6 weeks
Trial registration:	Not documented
Study Population	Participants: Zafirlukast group, n=180; placebo group, n=188 Eligibility criteria: age 17 to 71 years; asthma diagnosis according to GINA criteria and NHLBI guidelines; patient were required to have not smoked during the preceding 6 months; FEV1% predicted of 50% to 75%, a reversibility PEFR or FEV1 of ≥15% after inhalation of ≤400 mg albuterol, and current therapy with inhaled corticosteroids (beclomethasone ≥1,200 mg/day or equivalent)
Setting	United Kingdom
Interventions	Zafirlukast 80 mg twice daily, placebo for 6 weeks
Adherence reported	No
Primary outcomes	The change in mean morning PEFR from baseline to week 6
Secondary outcomes	The change in mean evening PEFR, FEV1 daytime symptom score, SABA use from baseline to week 6 risk of an exacerbation of asthma

Study reference	Wang (Cordyceps sinensis) 2016
Study title	Herbal medicine cordyceps sinensis improves health-related quality of life in moderate-to-severe asthma
Study duration	3 months
Trial registration:	ChiCTR-IPC-16008730
Study Population	Participants: cordyceps group, n=60; control group, n=60 Eligibility criteria: age ≥ 18 years; moderate or severe asthma with evidence of fixed airflow obstruction following a trial of maximum bronchodilator therapy and a trial of oral corticosteroids of at least 3-week duration
Setting	China
Interventions	Cordyceps sinensis (1.2 g, 3 times per day, Corbrin capsule, Hangzhou Huadong Pharmaceutical Co. Ltd.) in addition to ICS/LABA or placebo
Adherence reported	No
Primary outcomes	AQLQ 1 day before, 1 day after, and 3 months after the intervention period
Secondary outcomes	FEV1, PEFR, and FEV1/FVC, and serum IgG, IgE, MMP9, IFN-γ, IL-4, and ICAM-1 levels were evaluated before and after the treatment period

Study reference	Wenzel (Nebulized dehydroepi-androsterone-3-sulfate) 2010
Study title	Nebulised Nebulized dehydroepi-androsterone-3-sulfate
Study duration	5-week run-in period. 6weeks
Trial registration:	ANZCTR: 012607000192482
Study Population	Participants: Nebulised Nebulized dehydroepi-androsterone-3-sulfate group, n=140; placebo group, n=140 Eligibility criteria**:** Patients 18-70 years of age, with ≥1-year history of asthma and FEV1% predicted of ≥60 at screening , ≥3 month of therapy with ≥500µg of fluticasone equivalent +LABA , rescue ß-agonist use within the past month , non-smoking for ≥1 year, and a total pack-year smoking history of <10years
Setting	20 sites in Australia and 14 sites in India
Interventions	70mg GenaFlow(Nebulised Nebulized dehydroepi-androsterone-3-sulfate) once daily or placebo
Adherence reported	No
Primary outcomes	Median change from baseline ACQ at 6 weeks
Secondary outcomes	Proportions of patients who achieved a minimally important difference of -0.5 in ACQ and the average change in ACQ

Study reference	Wenzel (Golimumab) 2009
Study title	A Randomized, Double-blind, Placebo-controlled Study of Tumor Necrosis Factor-a Blockade in Severe Persistent Asthma
Study duration	2-week run-in period. 52 weeks
Trial registration:	NCT00207740
Study Population	Participants: golimumab 200mg group, n=78; golimumab100mg group, n=76; golimumab 50mg group, n=77;placebo group, n=78 Eligibility criteria: age ≥18 years; diagnosed with asthma for ≥3 years; uncontrolled severe asthma for ≥1 years: symptomatic despite (asthma symptoms on more than one-third of days for 3 or more months before screening) despite continuous treatment with high-dose ICS (fluticasone >1000 mg or equivalent) and LABA, with or without continuous oral corticosteroids (OCS); two or more asthma exacerbations within the previous year; 1 or more years without smoking and a smoking history of less than 10 pack-years and a history of at least one of the following within 5 years of screening: postbronchodilator reversibility in FEV1 of ≥12%, or PEFR diurnal variation of ≥30% or BHR
Setting	United Kingdom, France, Poland, Hungary, France, The Netherlands, Hungary and Italy
Interventions	Subcutaneous injections of placebo, 50 mg golimumab (75 mg loading dose at baseline), 100 mg golimumab (150 mg at baseline), or 200 mg golimumab (300 mg at baseline) were given every 4 weeks for 52 weeks

Adherence reported	No
Primary outcomes	The change in prebronchodilator percent predicted FEV1 and number of severe asthma exacerbations from baseline through week 24
Secondary outcomes	The change from baseline through week 24 in the AQLQ score, rescue medication use, and domiciliary morning PEFR

Study reference	Wenzel (Dupilumab) 2013
Study title	Dupilumab in persistent asthma with elevated eosinophil levels
Study duration	2-week screening period. 20 weeks
Trial registration:	NCT01312961
Study Population	Participants: Dupilumab group, n=52; Placebo group, n=52 Eligibility criteria: age 18 to 65 years old; persistent, moderate-to-severe asthma; elevated blood eosinophil count (≥300 cells per microliter) or an elevated sputum eosinophil level (≥3%) at screening; asthma symptoms that were not well controlled with medium-dose to high-dose ICS plus LABAs (fluticasone [≥250 µg] and salmeterol [50 µg] twice daily or the equivalent)
Setting	United States
Interventions	Once weekly subcutaneous injections of dupilumab (300 mg) or placebo for 12 weeks
Adherence reported yes/no	No
Primary outcomes	The occurrence of an asthma exacerbation, during the 12-week intervention period
Secondary outcomes	The time to an asthma exacerbation and the change from baseline at each visit and at week 12 in FEV1, morning and evening PEF, ACQ5 score, morning and evening asthma symptom scores nocturnal awakenings, and the number of albuterol or levalbuterol inhalations per day

Appendix 3: Risk of bias summary for all included trials.

The table is composed of the consensus opinion of the review authors' judgements about each methodological quality item**.**

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Ayres (Omalizumab) 2004	?	?	+	+	-	-	-
Bardelas (Omalizumab) 2012	?	?	?	?	-	-	-
Beeh (Tiotropium) 2014	-	-	?	?	-	-	-
Bel (Mepolizumab) 2014	-	-	-	-	-	-	-
Berry (Eternacept) 2006	-	?	?	?	-	-	-
Bjermer (Reslizumab) 2016	?	?	?	?	-	-	-
Bleecker (Benralizumab) 2016	-	-	-	-	-	-	-
Brightling (Tralokinumab) 2015	-	-	-	-	-	-	-

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Brinke (IM triamcinolone) 2004	?	?	?	?	-	-	-
Brusselle (Azithromycin) 2013	-	?	?	?	-	-	-
Busse (Omalizumab) 2001	?	?	?	?	-	-	-
Busse (Brodalumab) 2013	-	-	?	?	-	-	-
Busse (Daclizumab) 2008	?	?	?	?	-	-	-
Busse (AMG 853) 2013	?	?	?	?	-	-	-
Cahill (Imatinib) 2017	?	?	?	?	-	-	-
Castro (Bronchial thermoplasty) 2010	-	?	-	-	-	-	-
Castro (Benralizumab) 2014	-	-	-	?	-	-	-
Castro (Reslizumab) 2015	-	-	-	-	-	-	-

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Castro (Reslizumab) 2011	-	-	-	-	-	-	-
Chanez (Omalizumab) 2010	?	?	-	?	-	-	-
Corren (AMG 317) 2010	-	?	?	?	-	-	-
Corren (Lebrikizumab) 2011	-	-	-	-	-	-	-
Corren (Reslizumab) 2016	?	?	-	-	-	-	+
Cox (Bronchial thermoplasty) 2007	-	?	+	+	-	-	-
Coyle (Bosentan) 2013	-	-	-	?	-	-	-
DeBoever (GSK679586) 2014	-	-	-	-	-	-	-
Dente (Prednisolone) 2010	?	?	?	?	-	-	-
Erin (Infiliximab) 2006	?	?	-	-	-	-	-

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Fernandes (Prednisolone) 2014	-	?	?	?	-	-	-
FitzGerald (Benralizumab) 2016	-	-	-	?	-	-	-
Flood-Page (Mepolizumab) 2007	?	?	-	?	-	-	-
Gao J-M (Montelukast) 2013	?	?	?	?	-	-	-
Garcia (Omalizumab) 2013	-	?	?	?	-	-	-
Gevaert (Omalizumab) 2013	-	?	-	?	-	+	-
Girodet (Gallopamil) 2015	-	-	-	-	-	-	-
Gotfried (Clarithromycin) 2004	?	?	?	?	+	+	-
Haldar (Mepolizumab) 2009	-	?	-	-	-	-	-

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Hanania (Omalizumab) 2011	-	-	-	-	-	-	-
Hanania (Lebrikizumab) 2015	-	-	-	-	-	-	-
Hanania (Lebrikizumab) 2016	-	-	-	?	-	-	-
Hedman (Methotrexate) 1996	?	?	?	?	-	-	-
Hodgson (Ciclesonide) 2015,	?	?	?	?	-	-	-
Holgate (Omalizumab) 2004	?	?	?	?	-	-	-
Holgate (Etanercept) 2011	?	?	?	?	-	-	-
Humbert (Omalizumab) 2005	?	?	-	-	-	-	-
Humbert (Masitinib) 2009	?	?	?	?	-	-	-

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Juergens (Eucalyptol) 2003	-	-	-	?	-	-	-
Kaler (Pioglitazone) 2017	-	-	-	?	-	-	-
Kanzow (Methotrexate) 1995	?	?	?	?	-	-	-
Kenyon (L-Arginine) 2011	?	?	-	?	-	-	-
Kerstjens (Tiotropium) 2011	-	?	?	?	-	-	-
Kerstjens (Tiotropium) 2015	-	?	-	?	-	-	-
Kishiyama (IVIG) 1999	?	?	?	-	+	-	-
Lanier (Omalizumab) 2003	?	?	?	?	-	-	-
Laviollette (Benralizumab) 2013	-	?	?	?	-	-	-
Li (Omalizumab) 2014	-	?	?	?	-	-	-
Lock (Ciclosporin) 1996	?	?	-	-	-	-	-

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Lomia (Carbamazepine) 2006	-	-	-	?	-	-	-
Marin (Nedocromil sodium) 1996	-	?	?	?	-	-	-
Morjaria (Etanercept) 2008	?	?	?	?	-	-	-
Nair (SCH 527123) 2012	?	?	?	?	-	-	-
Nair (Mepolizumab) 2009	-	-	-	-	-	-	-
Nair (Benralizumab) 2017	-	-	?	-	-	-	-
Nizankowska (Ciclosporin) 1995	?	?	-	-	-	-	-
Ogirala (IM triamcinolone) 1995	?	?	?	?	-	-	-
Oh (MEDI528) 2013	-	-	?	?	-	-	-
Ohta (Omalizumab) 2009	?	?	?	?	-	-	-

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Ortega (Mepolizumab) 2014	-	-	-	-	-	-	-
Park (Benralizumab) 2016	-	?	?	?	-	-	-
Pavord (Bronchial thermoplasty) 2007	-	?	+	+	?	-	-
Pavord (Mepolizumab) 2012	-	-	-	-	-	-	-
Piper (Tralokinumab) 2013	?	?	?	?	-	-	-
Robinson (Montelukast) 2001	?	-	?	?	-	-	-
Rubin (Omalizumab) 2012	?	?	+	+	-	-	-
Salmun (IVIG) 1999	-	?	-	?	?	-	-
Sano (Sodium cromoglicate) 2006	-	?	-	?	-	-	-
Bosquet (Omalizumab) 2011	-	?	?	?	-	-	-

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Simpson (Clarithromycin) 2008	-	?	-	?	-	-	-
Smith (Isoflavane) 2015	-	-	-	-	-	-	-
Soler (Omalizumab) 2001	?	?	?	?	-	-	-
Tamaoki (Th2 inhibitor IL5/IL4) 2000	-	-	?	?	-	-	-
Vignola (Omalizumab) 2004	?	?	?	?	-	-	-
Virchow (Zafirlukast) 2000	?	?	?	?	-	-	-
Wang (Cordyceps sinensis) 2016	?	?	?	?	-	-	-
Wenzel (Nebulized dehydroepi-androsterone-3-sulfate) 2010	?	?	?	?	?	-	-
Wenzel (Golimumab) 2009	-	?	?	-	-	-	-

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants & personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Selection bias)	Other bias
Wenzel (Dupilumab) 2013	-	-	-	-	-	-	-
'?' = unclear risk of bias (ROB), '-' = low ROB, '+' = high ROB							

Appendix 4 Secondary outcomes

Study or Subgroup	Active add-on therapy Mean	SD	Total	Placebo add-on therapy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bjermer (Reslizumab) 2015	0.286	0.553	102	0.126	0.557	103	3.2%	0.16 [0.01, 0.31]
Brightling (Tralokinumab) 2015	0.117	0.422	130	0.007	0.402	125	7.1%	0.11 [0.01, 0.21]
Hanania Lavolta I (Lebikizumab 125mg Th2 low)	0.15	0.317	92	0.025	0.311	89	8.7%	0.13 [0.03, 0.22]
Hanania Lavolta I (Lebrikizumab 125mg Th2 high)	0.211	0.372	222	0.098	0.366	214	15.2%	0.11 [0.04, 0.18]
Hanania Lavolta I (Lebrikizumab 37.5mg Th2 high)	0.201	0.378	229	0.098	0.366	214	15.2%	0.10 [0.03, 0.17]
Hanania Lavolta I (Lebrikizumab 37.5mg Th2 low)	0.038	0.306	92	0.025	0.311	89	9.0%	0.01 [-0.08, 0.10]
Hanania Lavolta II (Lebirkizumab 37.5mg Th2 low)	0.088	0.392	83	0.087	0.382	87	5.4%	0.00 [-0.12, 0.12]
Hanania Lavolta II (Lebrikizumab 125mg Th2 high)	0.179	0.371	221	0.096	0.37	219	15.2%	0.08 [0.01, 0.15]
Hanania Lavolta II (Lebrikizumab 125mg Th2 low)	0.107	0.388	90	0.087	0.382	87	5.7%	0.02 [-0.09, 0.13]
Hanania Lavolta II lebrikizumab 37.5mg Th2 high)	0.184	0.38	231	0.096	0.37	219	15.2%	0.09 [0.02, 0.16]
Total (95% CI)			**1492**			**1446**	**100.0%**	**0.09 [0.06, 0.11]**

Heterogeneity: Chi² = 8.53, df = 9 (P = 0.48); I² = 0%
Test for overall effect: Z = 6.17 (P < 0.00001)

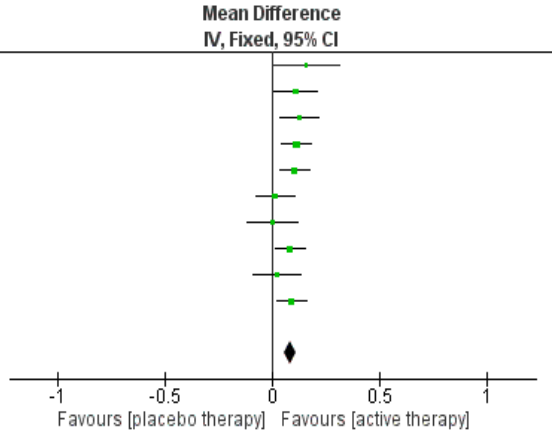


Figure 2.1 FEV1 (litres): Forest plot shows studies that used objective measures of adherence

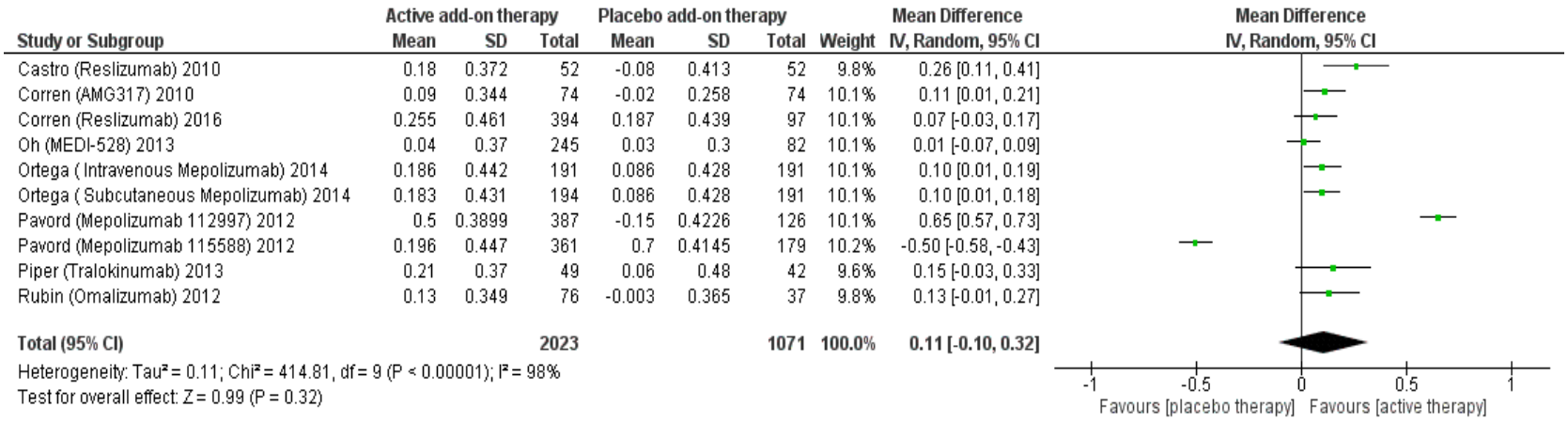
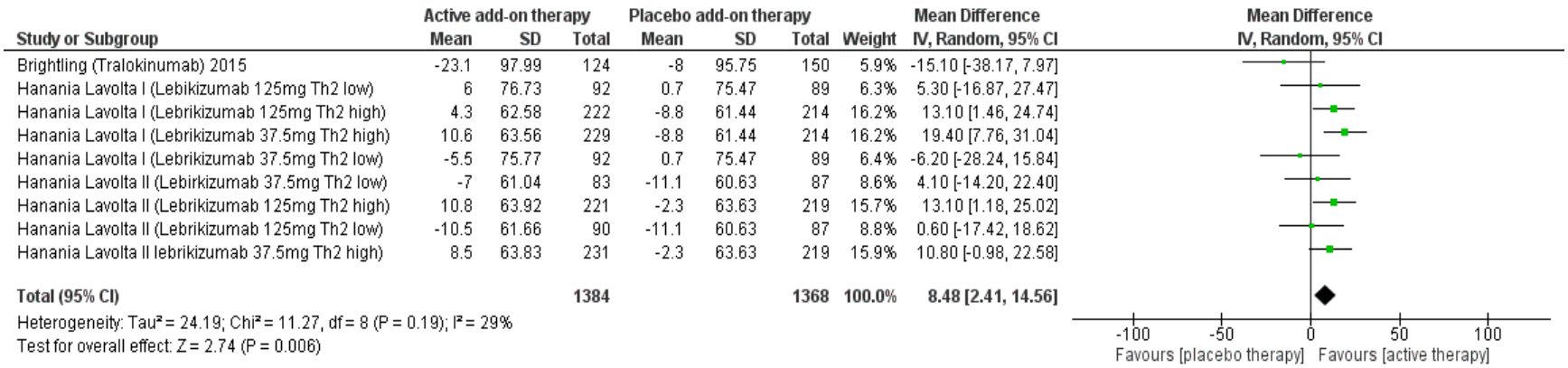


Figure 2.2

FEV1 (litres): Forest plot shows studies that did not report adherence to ICS/LABA therapy.



Figure

3.1 PEF (litres/minute): Forest plot shows studies that used objective measures of adherence.

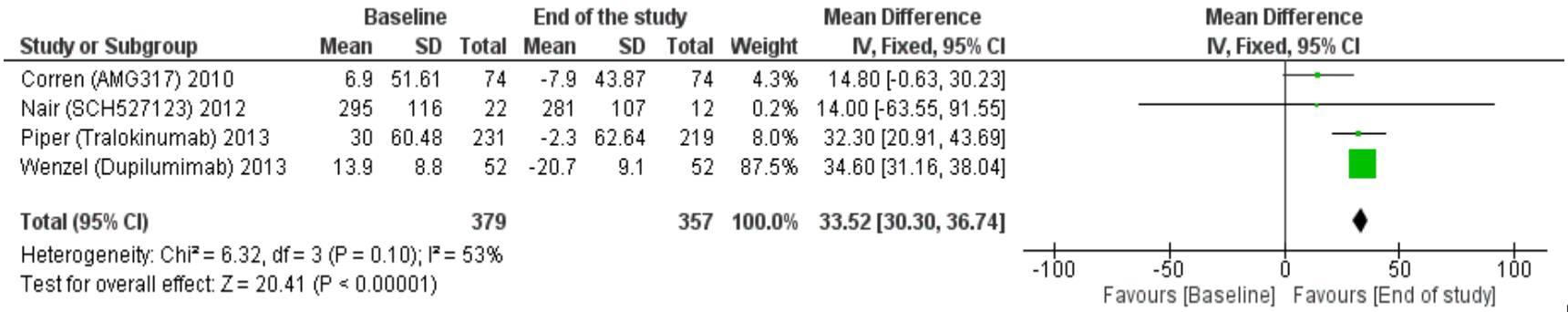


Figure 3.2

PEF (litres/minute): Forest plot shows studies that did not report adherence to ICS/LABA therapy

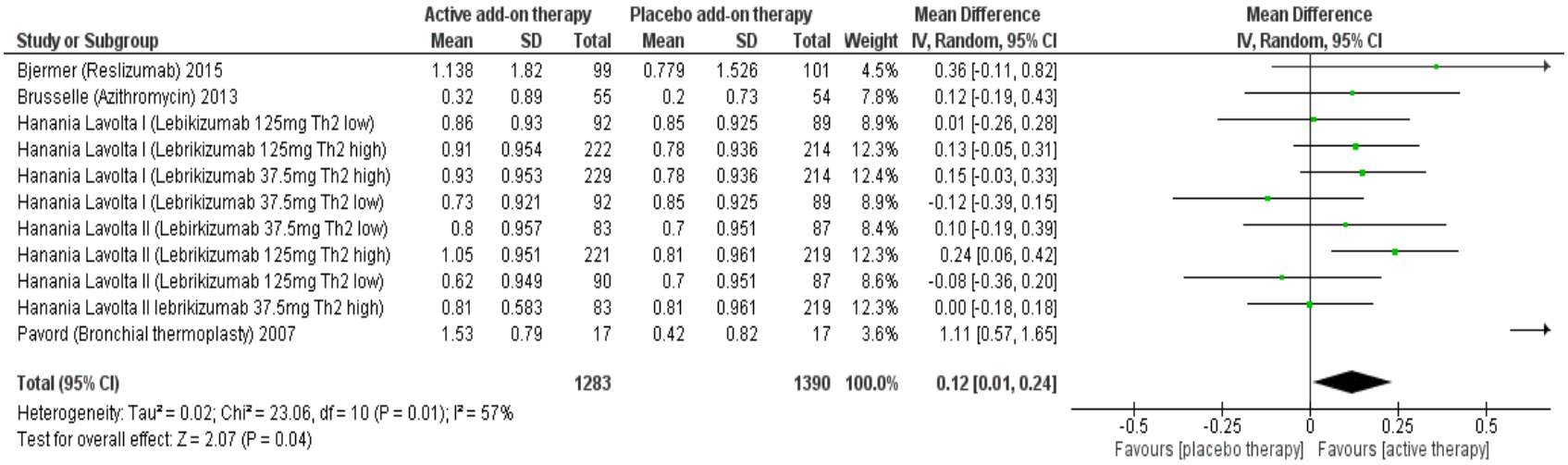


Figure 4.1

AQLQ: Forest plot shows studies that used objective measures of adherence

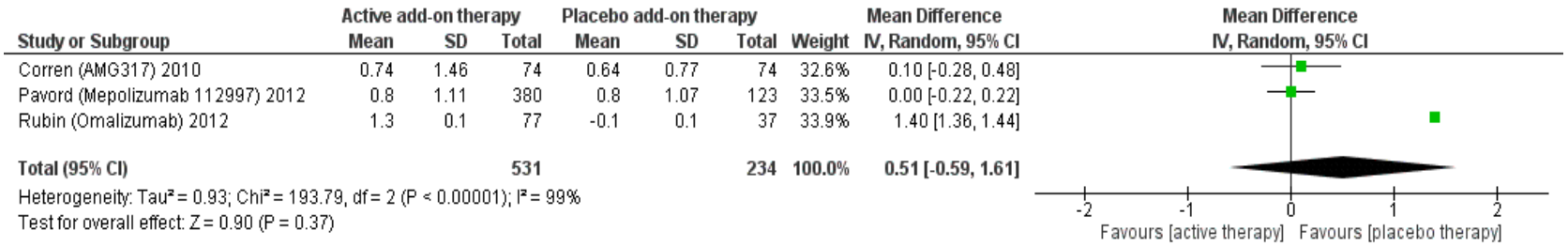


Figure 4.2

AQLQ: Forest plot shows studies that did not report adherence to ICS/LABA therapy

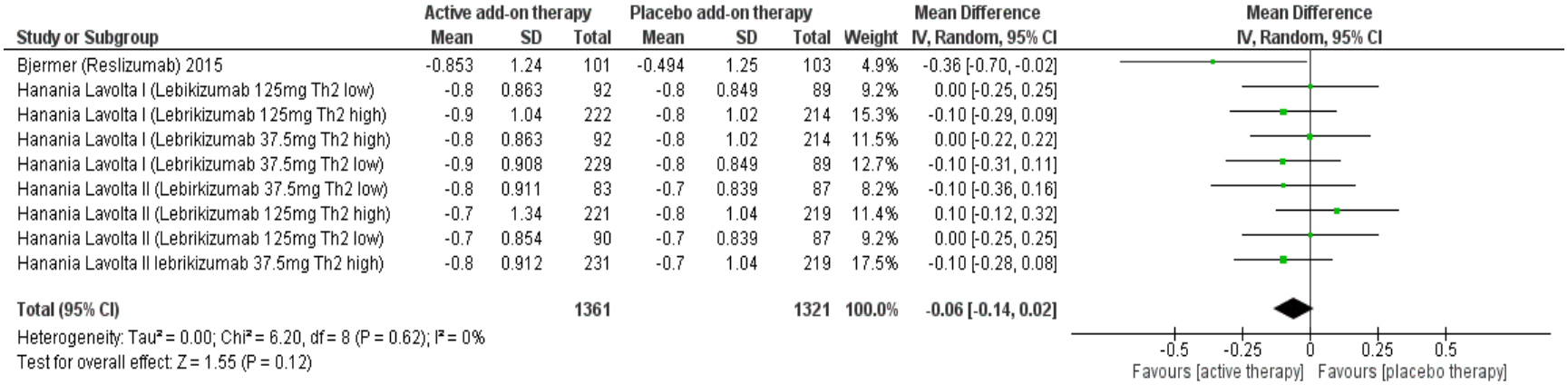


Figure5.1

ACQ: Forest plot shows studies that used objective measures of adherence

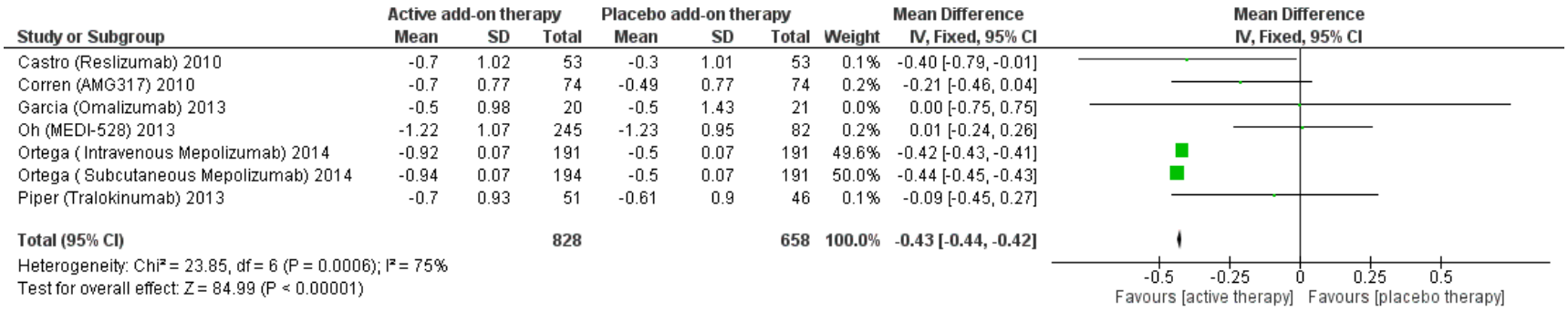


Figure 5.2

ACQ: Forest plot shows studies that did not report adherence to ICS/LABA therapy.

ASSESSMENT OF THE PLACEBO EFFECT

Study or Subgroup	End of study Mean	SD	Total	Baseline Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Berry (Etanercept) 2006	2.22	0.8	10	2.6	0.9	10	2.1%	-0.38 [-1.13, 0.37]
Bjermer (Reslizumab) 2015	2.32	0.792	105	2.22	0.183	105	7.6%	0.10 [-0.06, 0.26]
Busse (Daclizumab) 2008	2.2	0.1	27	2.25	0.1	27	8.4%	-0.05 [-0.10, 0.00]
Castro (Reslizumab NCT 01285323) 2015	2.1	0.695	232	2	0.668	232	7.9%	0.10 [-0.02, 0.22]
Castro (Reslizumab NCT 01287039) 2015	2.02	0.817	244	1.93	0.791	244	7.7%	0.09 [-0.05, 0.23]
Corren (Reslizumab) 2016	2.34	0.72	97	2.17	0.633	97	7.1%	0.17 [-0.02, 0.36]
DeBoever GSK679586 2014	2.015	0.736	91	2	0.746	99	6.9%	0.02 [-0.20, 0.23]
Dente (Prednisolone) 2010	1.78	0.55	20	1.84	0.57	20	5.2%	-0.06 [-0.41, 0.29]
Gao Jin-Ming (Montelukast) 2013	2.29	0.15	22	1.72	0.16	22	8.2%	0.57 [0.48, 0.66]
Hodgson (Ciclesonide) 2015	2	0.6	15	2.1	0.7	15	3.9%	-0.10 [-0.57, 0.37]
Kerstjens (Tiotropium) 2011	1.802	0.574	101	1.733	0.589	107	7.5%	0.07 [-0.09, 0.23]
Lomia (Carbamazepine) 2006	1.23	0.58	37	1.2	0.55	37	6.3%	0.03 [-0.23, 0.29]
Nair (Mepolizumab) 2009	2.3	0.4	2	2.2	0.9	11	2.0%	0.10 [-0.67, 0.87]
Nair (SCH527123) 2012	2.1	0.9	22	1.7	0.5	12	3.9%	0.40 [-0.07, 0.87]
Pavord (Mepolizumab 112997) 2012	1.969	0.7295	127	1.882	0.6126	127	7.4%	0.09 [-0.08, 0.25]
Pavord (Mepolizumab 115588) 2012	1.94	0.6126	179	1.87	0.6295	161	7.8%	0.07 [-0.06, 0.20]
Total (95% CI)			**1331**			**1326**	**100.0%**	**0.10 [-0.03, 0.23]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 137.84$, df = 15 ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect: $Z = 1.55$ ($P = 0.12$)

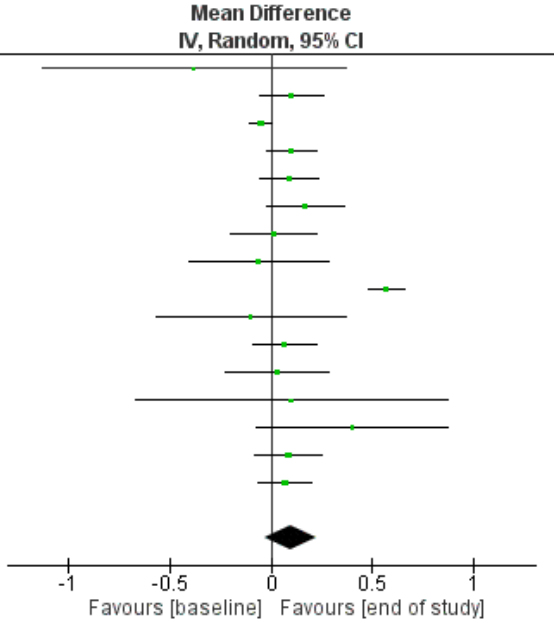


Figure 6 FEV1 (litres) placebo effect comparisons: Forest plot shows the effects of placebo on FEV1 in the control/placebo groups.

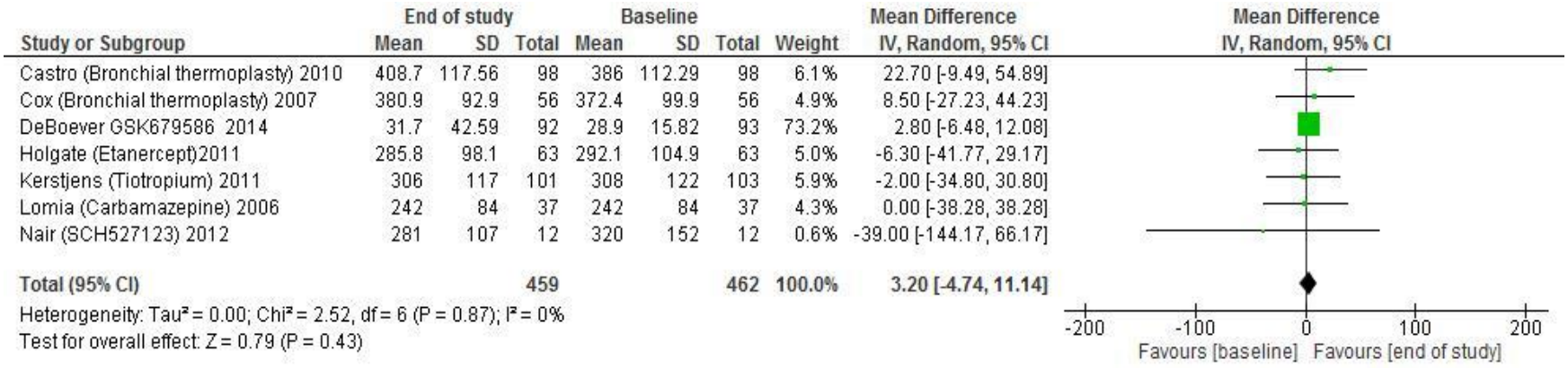


Figure 7 PEF (litres/minute): Forest plot shows the effects of placebo on PEF in the control/placebo groups.

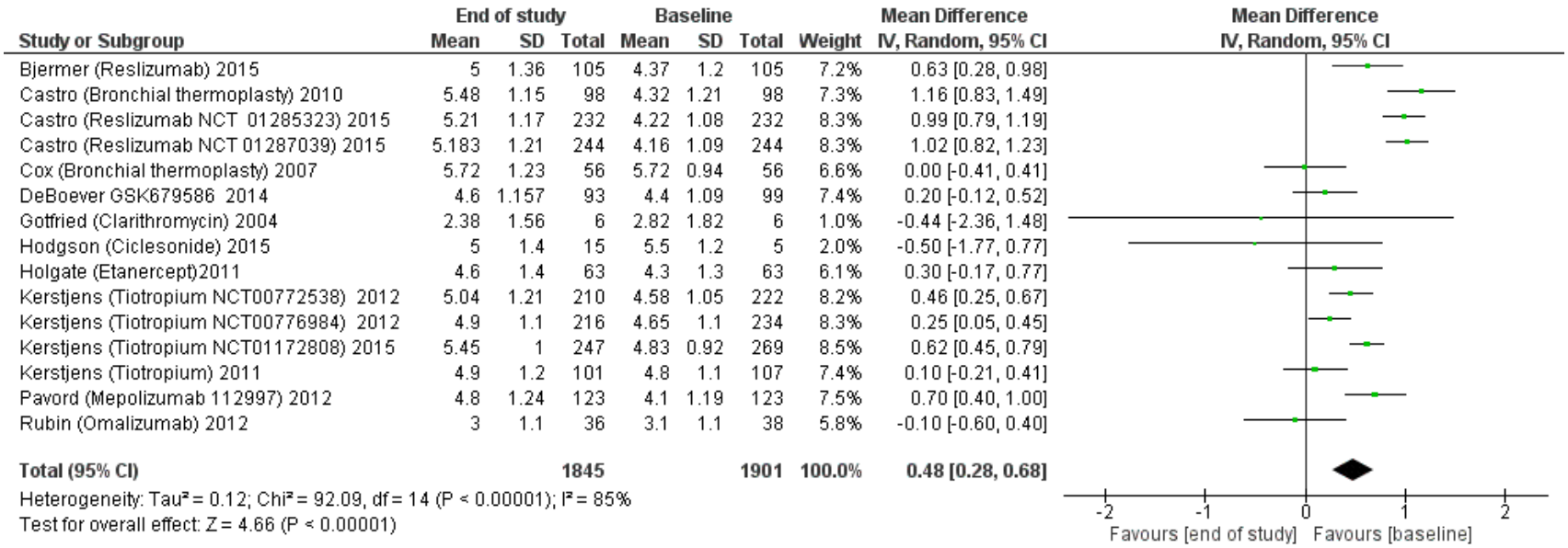


Figure 8 AQLQ: Forest plot shows the effects of placebo on AQLQ in the control/placebo groups.

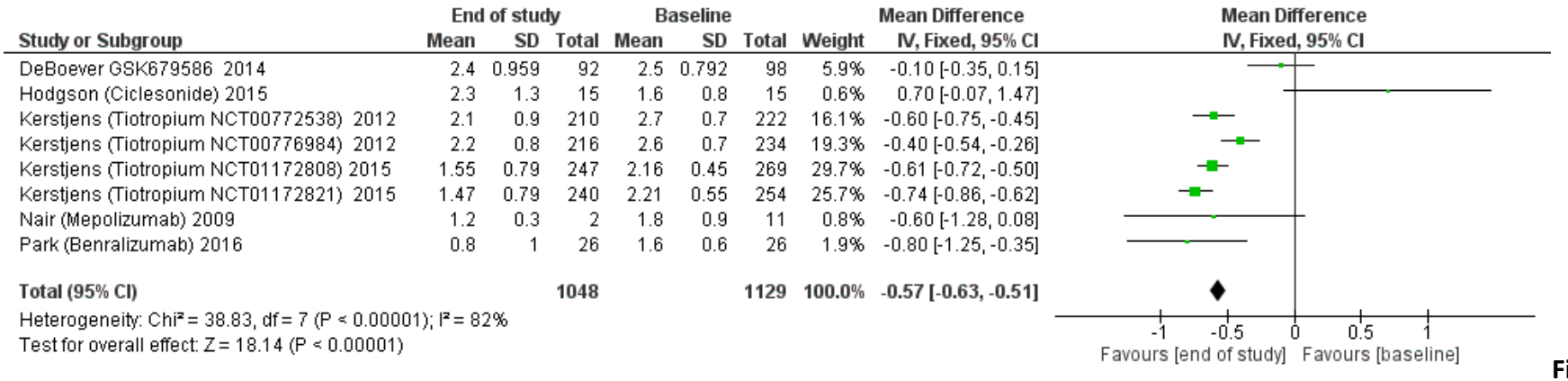


Figure 9

ACQ: Forest plot shows the effects of placebo on ACQ in the control/placebo groups.

Study or Subgroup	Active add-on therapy Mean	SD	Total	Placebo add-on therapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bjermer (Reslizumab) 2015	0.286	0.553	102	0.126	0.557	103	4.7%	0.16 [0.01, 0.31]
Brightling (Tralokinumab) 2015	0.117	0.422	130	0.07	0.402	125	5.0%	0.05 [-0.05, 0.15]
Castro (Reslizumab) 2010	0.18	0.372	52	-0.08	0.413	52	4.7%	0.26 [0.11, 0.41]
Corren (AMG317) 2010	0.09	0.344	74	-0.02	0.258	74	5.0%	0.11 [0.01, 0.21]
Corren (Reslizumab) 2016	0.255	0.461	394	0.187	0.439	97	5.0%	0.07 [-0.03, 0.17]
Hanania Lavolta I (Lebikizumab 125mg Th2 low)	0.15	0.317	92	0.025	0.311	89	5.1%	0.13 [0.03, 0.22]
Hanania Lavolta I (Lebrikizumab 125mg Th2 high)	0.211	0.372	222	0.098	0.366	214	5.1%	0.11 [0.04, 0.18]
Hanania Lavolta I (Lebrikizumab 37.5mg Th2 high)	0.201	0.378	229	0.098	0.366	214	5.1%	0.10 [0.03, 0.17]
Hanania Lavolta I (Lebrikizumab 37.5mg Th2 low)	0.038	0.306	92	0.025	0.311	89	5.1%	0.01 [-0.08, 0.10]
Hanania Lavolta II (Lebirkizumab 37.5mg Th2 low)	0.088	0.392	83	0.087	0.382	87	4.9%	0.00 [-0.12, 0.12]
Hanania Lavolta II (Lebrikizumab 125mg Th2 high)	0.179	0.371	221	0.096	0.37	219	5.1%	0.08 [0.01, 0.15]
Hanania Lavolta II (Lebrikizumab 125mg Th2 low)	0.107	0.388	90	0.087	0.382	87	5.0%	0.02 [-0.09, 0.13]
Hanania Lavolta II lebrikizumab 37.5mg Th2 high)	0.184	0.38	231	0.096	0.37	219	5.1%	0.09 [0.02, 0.16]
Oh (MEDI-528) 2013	0.04	0.37	245	0.03	0.3	82	5.1%	0.01 [-0.07, 0.09]
Ortega (Intravenous Mepolizumab) 2014	0.186	0.442	191	0.086	0.428	191	5.1%	0.10 [0.01, 0.19]
Ortega (Subcutaneous Mepolizumab) 2014	0.183	0.431	194	0.086	0.428	191	5.1%	0.10 [0.01, 0.18]
Pavord (Mepolizumab 112997) 2012	0.128	0.42	390	0.87	0.4639	127	5.1%	-0.74 [-0.83, -0.65]
Pavord (Mepolizumab 115588) 2012	0.196	0.447	361	0.7	0.4149	179	5.1%	-0.50 [-0.58, -0.43]
Piper (Tralokinumab) 2013	0.21	0.37	49	0.06	0.48	42	4.6%	0.15 [-0.03, 0.33]
Rubin (Omalizumab) 2012	0.13	0.349	76	-0.003	0.365	37	4.8%	0.13 [-0.01, 0.27]
Total (95% CI)			**3518**			**2518**	**100.0%**	**0.02 [-0.09, 0.13]**

Heterogeneity: Tau² = 0.06; Chi² = 501.16, df = 19 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.36 (P = 0.72)

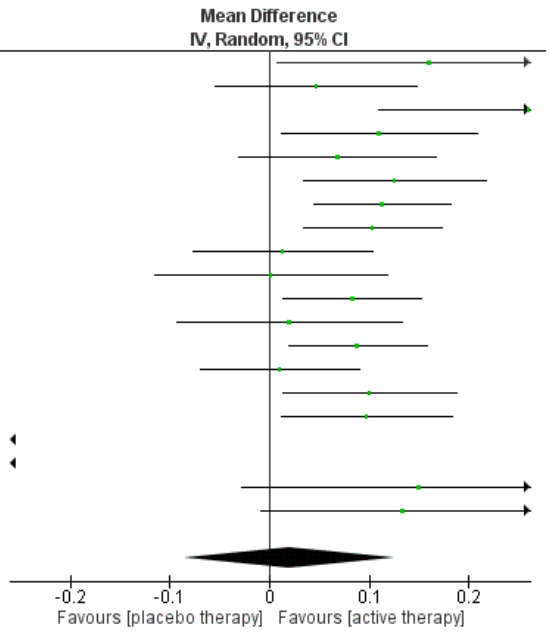


Figure 10.1 FEV1 (litres). Forest plot shows study results of included studies.

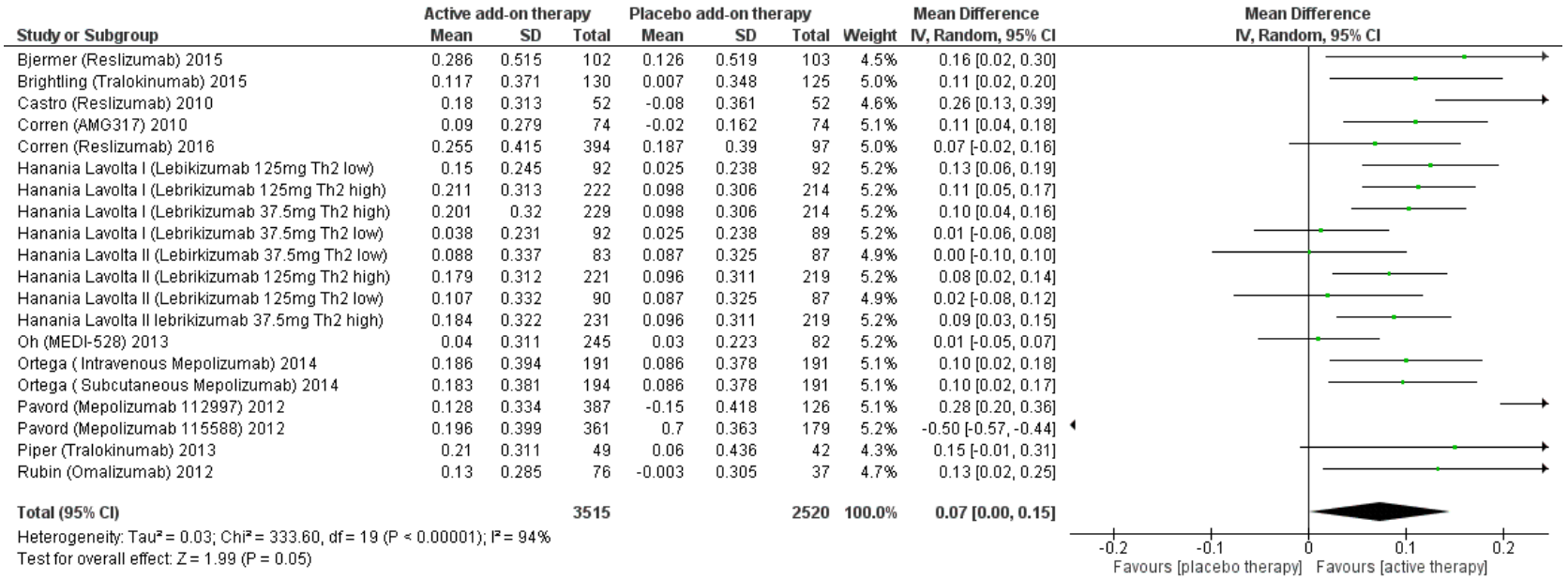


Figure 10.2: Forest plot show a model of the change in FEV1 (litres) corrected for adherence assessment at baseline

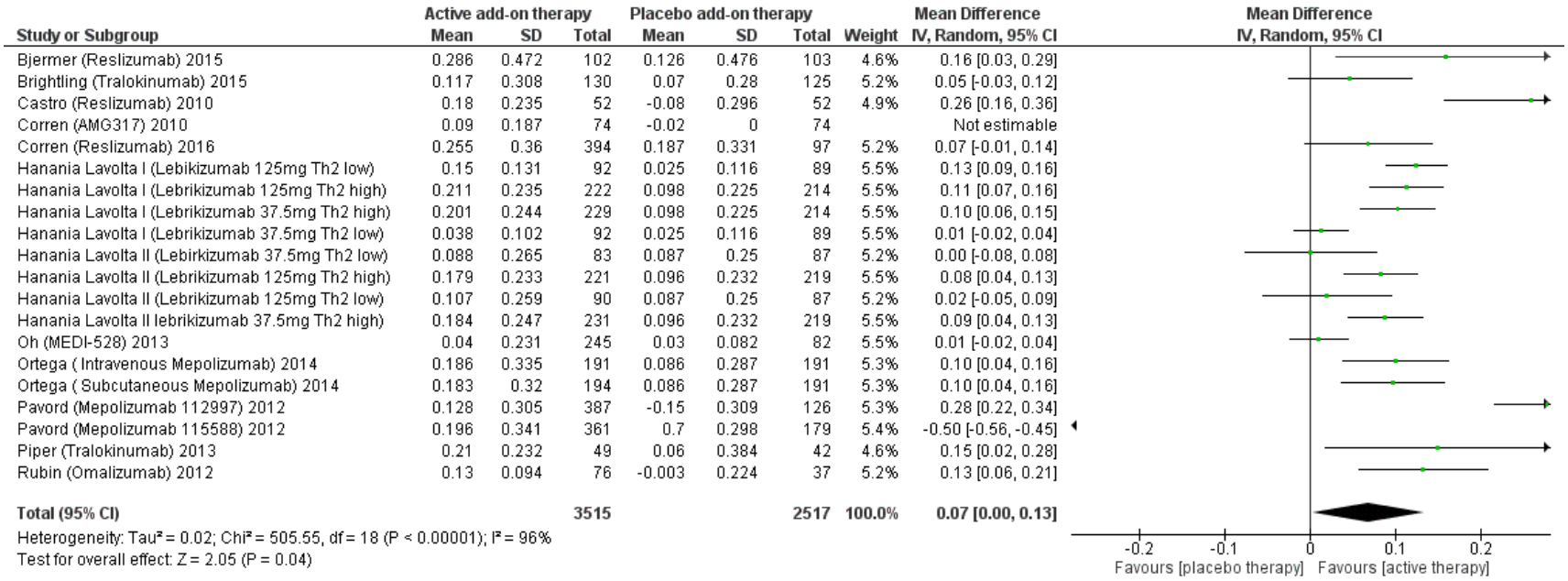


Figure 10.3: Forest plot showing the change in FEV1 (litres) corrected for variation in month to month adherence

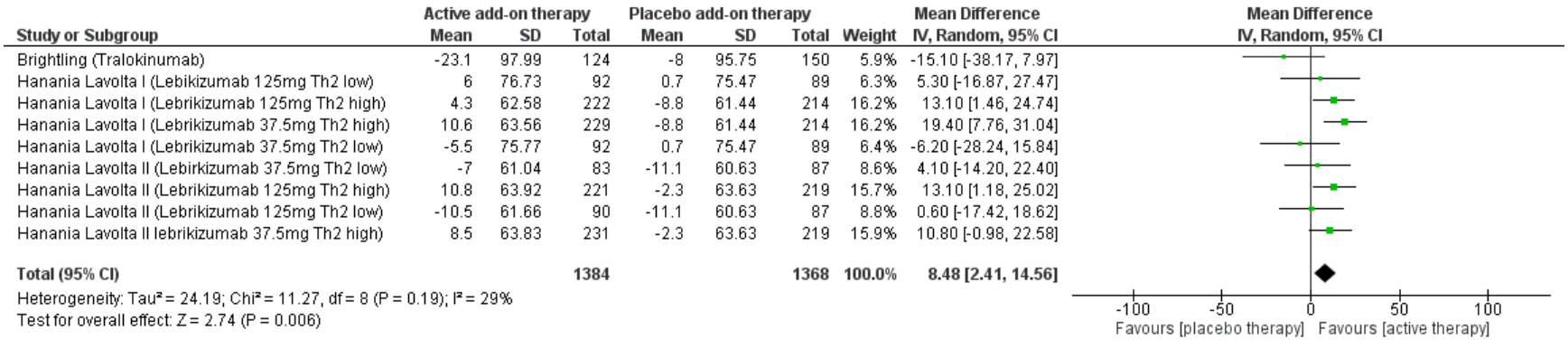


Figure 11.1: PEF (litres/minute). Forest plot shows study results of included studies.

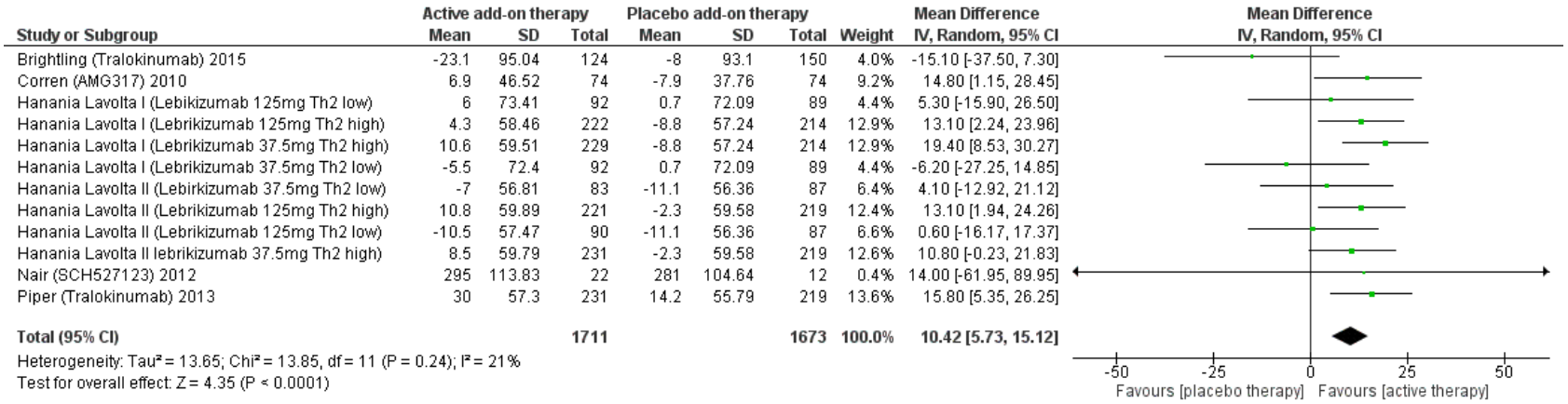


Figure 11.2: Forest plot show a model of the change in PEF (litres/minute) corrected for adherence assessment at baseline

Study or Subgroup	Active add-on therapy Mean	SD	Total	Placebo add-on therapy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Brightling (Tralokinumab) 2015	-23.1	92.57	124	-8	90.2	150	2.9%	-15.10 [-36.87, 6.67]
Corren (AMG317) 2010	6.9	40.39	74	-7.9	29.88	74	10.4%	14.80 [3.35, 26.25]
Hanania Lavolta I (Lebikizumab 125mg Th2 low)	6	69.68	92	0.7	68.29	89	3.4%	5.30 [-14.80, 25.40]
Hanania Lavolta I (Lebrikizumab 125mg Th2 high)	4.3	53.7	222	-8.8	52.37	214	13.7%	13.10 [3.14, 23.06]
Hanania Lavolta I (Lebrikizumab 37.5mg Th2 high)	10.6	54.84	229	-8.8	52.37	214	13.6%	19.40 [9.42, 29.38]
Hanania Lavolta I (Lebrikizumab 37.5mg Th2 low)	-5.5	68.62	92	0.7	68.29	89	3.4%	-6.20 [-26.15, 13.75]
Hanania Lavolta II (Lebirkizumab 37.5mg Th2 low)	-7	51.9	83	-11.1	51.42	87	5.6%	4.10 [-11.44, 19.64]
Hanania Lavolta II (Lebrikizumab 125mg Th2 high)	10.8	55.26	221	-2.3	54.92	219	12.8%	13.10 [2.81, 23.39]
Hanania Lavolta II (Lebrikizumab 125mg Th2 low)	-10.5	52.63	90	-11.1	51.42	87	5.8%	0.60 [-14.73, 15.93]
Hanania Lavolta II lebrikizumab 37.5mg Th2 high)	8.5	55.16	231	-2.3	54.92	219	13.1%	10.80 [0.63, 20.97]
Nair (SCH527123) 2012	295	111.46	22	281	102.06	12	0.2%	14.00 [-60.19, 88.19]
Piper (Tralokinumab) 2013	30	52.44	231	-2.3	50.79	219	15.0%	32.30 [22.76, 41.84]
Total (95% CI)			**1711**			**1673**	**100.0%**	**13.74 [10.06, 17.43]**

Heterogeneity: Chi² = 31.72, df = 11 (P = 0.0008); I² = 65%
Test for overall effect: Z = 7.30 (P < 0.00001)

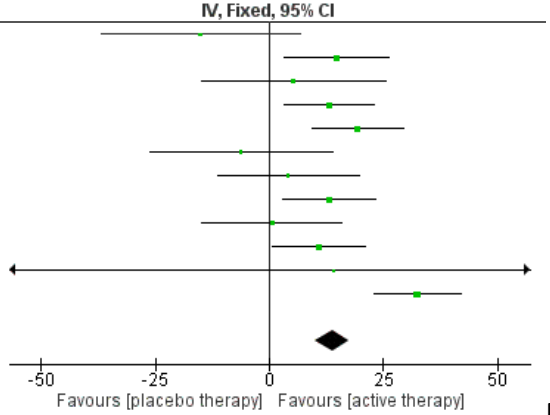


Figure 11.3: Forest plot showing the change in PEF (litres/minute) corrected for variation in month to month adherence

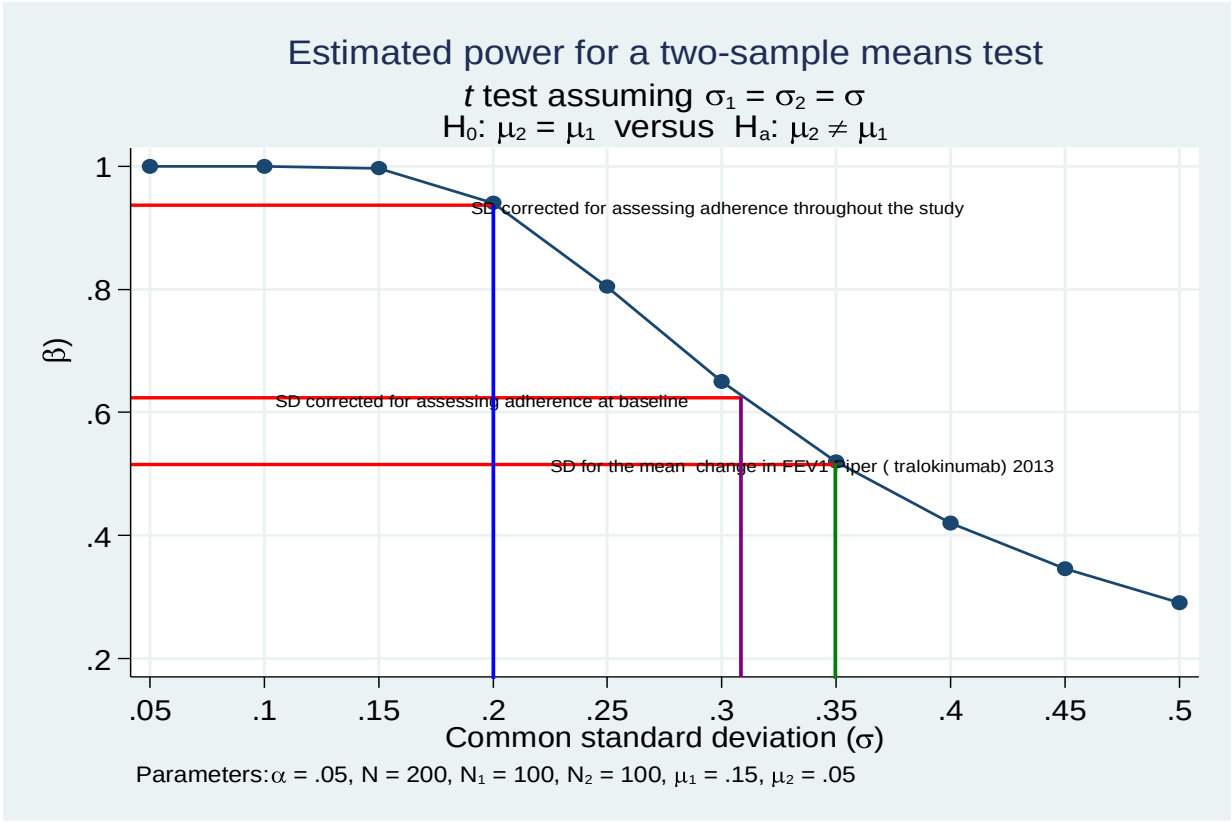


Figure 12: The graph shows the estimated power for two sample means, assuming standard deviation is the same for both the active add-on therapy and placebo add-on therapy. If adherence is not assessed the power of the study is significantly reduced. Assessment of adherence at baseline as well as throughout the conduct of the study results in an increased study power of approximately 95%.

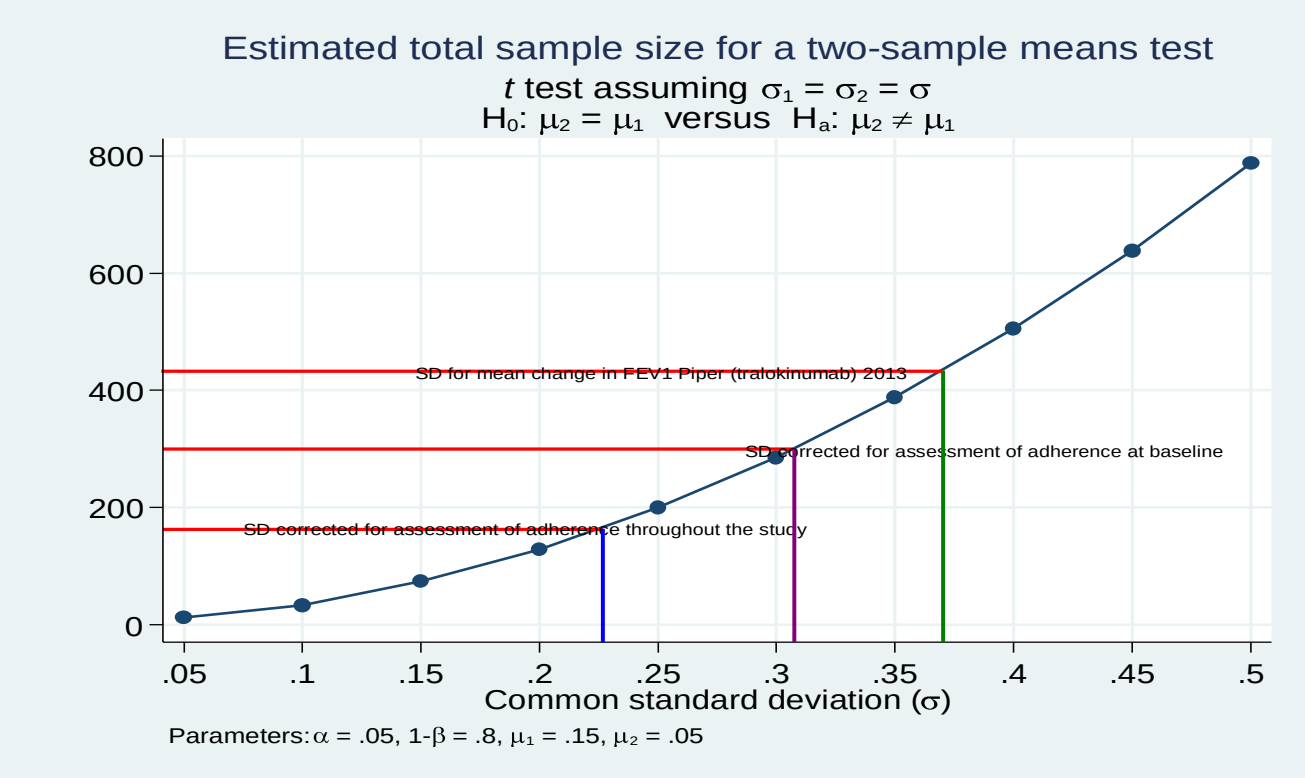


Figure 13: The graph shows the estimated power for sample size for two independent sample means, assuming standard deviation is the same for both the active add-on therapy and placebo add-on therapy. If adherence is not assessed a larger sample size is required and sample size can be decreased by assessing adherence at baseline as well as throughout the conduct of the study.

Appendix 5: Asthma Control Test (ACT) Questionnaire

Why take the Asthma Control Test™?

The Asthma Control Test™ will provide you with a snapshot of how well your asthma has been controlled over the last four weeks, giving you a simple score out of 25. Asthma symptoms can vary from month to month, so it is worth keeping the test handy to see if your score changes. You can also share your results with your doctor or asthma nurse to help explain just how your asthma affects you.

Are you in control of your asthma? Or is your asthma in control of you? Here's how to find out

Step 1: Read each question below carefully, circle your score and write it in the box.

Step 2: Add up each of your five scores to get your total Asthma Control Test™ score.

Step 3: Use the score guide to learn how well you are controlling your asthma.

Q1 During the **past 4 weeks,** how often did your asthma prevent you from getting as much done at work, school or home? — Score:

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

Q2 During the **past 4 weeks,** how often have you had shortness of breath? — Score:

More than once a day	Once a day	3-6 times a week	1-2 times a week	Not at all
1	2	3	4	5

Q3 During the **past 4 weeks,** how often did your asthma symptoms (wheezing, coughing, chest tightness, shortness of breath) wake you up at night or earlier than usual in the morning? — Score:

4 or more times a week	2-3 nights a week	Once a week	Once or twice	Not at all
1	2	3	4	5

Q4 During the **past 4 weeks,** how often have you used your reliever inhaler (usually blue)? — Score:

3 or more times a day	1-2 times a day	2-3 times a week	Once a week or less	Not at all
1	2	3	4	5

Q5 How would you rate your **asthma control** during the **past 4 weeks?** — Score:

Not controlled	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled
1	2	3	4	5

Total Score

What does your score mean?

Score: 25 – WELL DONE

- Your asthma appears to have been UNDER CONTROL over the last 4 weeks.
- However, if you are experiencing any problems with your asthma, you should see your doctor or nurse.

Score: 20 to 24 – ON TARGET

- Your asthma appears to have been REASONABLY WELL CONTROLLED during the past 4 weeks.
- However, if you are experiencing symptoms your doctor or nurse may be able to help you.

Score: less than 20 – OFF TARGET

- Your asthma may NOT HAVE BEEN CONTROLLED during the past 4 weeks.
- Your doctor or nurse can recommend an asthma action plan to help improve your asthma control.

Appendix 6: Mini Asthma Quality of Life Questionnaire (AQLQ)

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE (UNITED KINGDOM)
SELF-ADMINISTERED

PATIENT ID _____

DATE _____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

		All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
1.	Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
2.	Feel bothered by or have to avoid DUST in the environment?	1	2	3	4	5	6	7
3.	Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
4.	Feel bothered by COUGHING?	1	2	3	4	5	6	7
5.	Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
6.	Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?	1	2	3	4	5	6	7
7.	Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?	1	2	3	4	5	6	7
8.	Have DIFFICULTY GETTING A GOOD NIGHT'S SLEEP as a result of your asthma?	1	2	3	4	5	6	7
9.	Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
10.	Experience a WHEEZE in your chest?	1	2	3	4	5	6	7

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE (UNITED KINGDOM)
SELF-ADMINISTERED

PATIENT ID _____

DATE _____

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
11. Feel bothered by or have to avoid going outside because of WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** DOING THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
12. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
13. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
14. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
15. WORK-RELATED ACTIVITIES* (tasks you have to do at work)	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

DOMAIN CODE:

Symptoms: 1, 4, 6, 8, 10
Activity Limitation: 12, 13, 14, 15
Emotional Function: 3, 5, 9
Environmental Stimuli: 2, 7, 11

Appendix 7: European Quality of life, 5 dimensions, 3 layers (EQ-5D-3L) Questionnaire

Figure 1: EQ-5D-3L (UK English sample version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care
I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

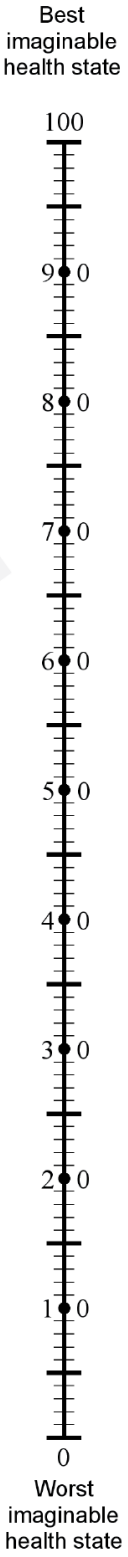
Pain/Discomfort
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked **100** and the worst state you can imagine is marked **0**.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 8: Work Productivity Impairment (WAPI)-Asthma Questionnaire

Work Productivity and Activity Impairment Questionnaire:
ASTHMA (WPAI:Asthma)

The following questions ask about the effect of your asthma on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your asthma? *Include hours you missed on sick days, times you went in late, left early, etc., because of your asthma. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your asthma affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If asthma affected your work only a little, choose a low number. Choose a high number if asthma affected your work a great deal.

Consider only how much asthma affected productivity while you were working.

Asthma had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	Asthma completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your asthma affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If asthma affected your activities only a little, choose a low number. Choose a high number if asthma affected your activities a great deal.

Consider only how much asthma affected your ability to do your regular daily activities, other than work at a job.

Asthma had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Asthma completely prevented me from doing my daily activities

CIRCLE A NUMBER

Appendix 9: Patient training manual

INCA
Inhaler
Compliance
Assessment

INCA
Inhaler
Compliance
Assessment

INCA SUN
Patient Training Manual

Date: _____

Patient Name: _____

1. Study Medications/Devices

Please take your medication and use your devices <u>EVERYDAY</u>

FeNo Machine 	**Once a day** (Do this test <u>before</u> taking Flixotide Inhaler) **** Do not do this test on the morning of Visit 2 as you will do it during the visit****
Peak Flow 	**3 blows** twice a day <u>before</u> inhalers **** No need to do this test on the morning of your visits****
Seretide Inhaler 500/50mcg or 250/50mcg 	**1 puff , twice a day** Please leave around 12 hours between each use. **** No need to take this on the morning of your visits****
Flixotide Inhaler 500mcg 	**2 puffs , once a day** (Do not take this inhaler until **<u>after</u>** doing FeNO test) ****Do not take this inhaler on the morning of Visit 2****
Ventolin Inhaler 200mcg 	**1 puff, As Needed**

2. FeNO Results

PLEASE RECORD DAILY

Device Number: _____

Date	FeNO Measurement	Time
Visit 1 **Day 0: __ / __ / __**		
Day 1 : __ / __ / __		
Day 2 : __ / __ / __		
Day 3 : __ / __ / __		
Day 4 : __ / __ / __		
Day 5 : __ / __ / __		
Day 6: __ / __ / __		

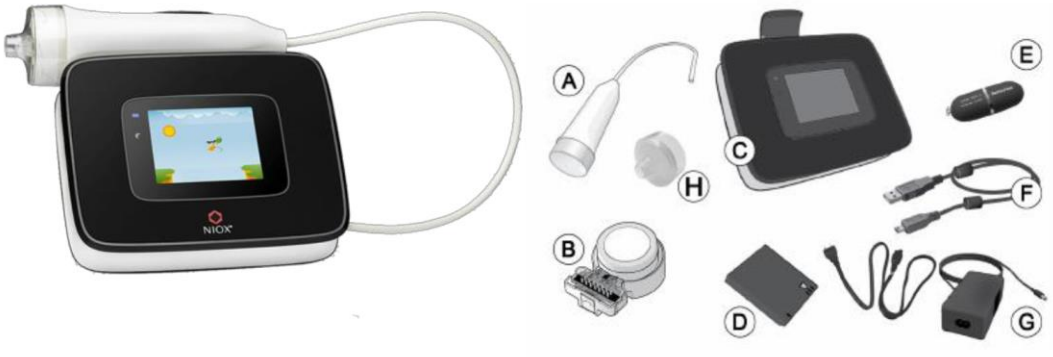
3. Participants Appointments

Study Visit Dates and Times

Visit Number	Date	Time	Rescheduled date and time
Visit 1	__/___/____		__/___/____
Visit 2 1 Week later	__/___/____		__/___/____
Visit 3 3 Weeks later	__/___/____		__/___/____
Visit 4 1 Month later	__/___/____		__/___/____
Dispensing Visit 1 1 Month later	__/___/____		__/___/____
Dispensing Visit 2 1 Month later	__/___/____		__/___/____
Visit 5 3 Months later	__/___/____		__/___/____
Dispensing Visit 3 1 Month later	__/___/____		__/___/____
Dispensing Visit 4 1 Month later	__/___/____		__/___/____
Visit 6 3 Months later	__/___/____		__/___/____

Please review your dates and times for following appointments to ensure that you can attend. Please contact the study nurse if an appointment must be cancelled and rescheduled. Remember each visit can only be rescheduled by 2 days max due to the doses on your inhaler

4. Participant Education- How to measure FeNO using the NIOX airway inflammation monitor



A) Breathing handle and handle cap, (B) Sensor (supplied separately),(C) Instrument (including stand), (D) Rechargeable battery, (E) NIOX PanelUSB memory stick, (F) USB cable, (G) Power adapter and power cord,(H) Patient filter (supplied separately)

Tips

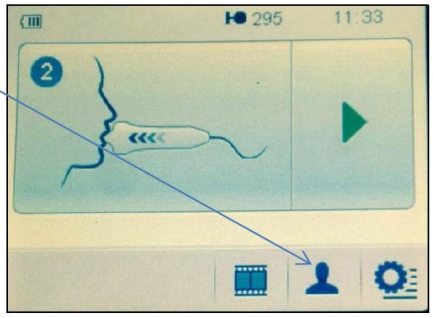
- **Keep mobile phones and cordless phones away from the device as it may cause interference with the results.** If you see the following error **A21** please turn off the machine remove any electronic devices or move to another room, turn back on the machine and repeat the test.

Guide: How to use?

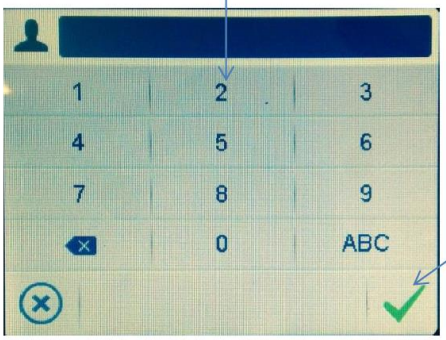
1. **Turn on the machine**: switch the button at the side of the machine or simply touch the screen if it is in standby.

5. **Enter your Study ID number** (this must be entered before each measurement):

   To do this, select the patient icon

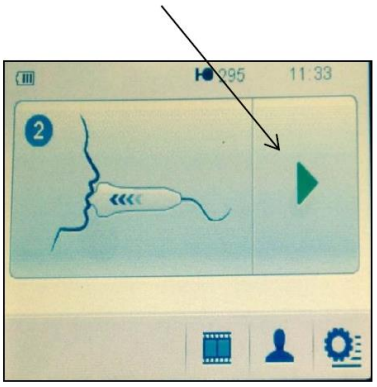


   Enter the ID number given to you by the nurse by selecting the numbers on the screen and then press the green arrow to save



6. Measuring FeNO
   A. Remove the cap cover and place a new filter onto the handle. The new filters will be in packages and should only be used once per person, **do not** remove the white cotton filter.

   B. Press the green start button to begin the test



   C. Exhale away from the mouthpiece to completely clear your lungs, then look at the screen and hold the machine up to your mouth.
   D. Close your lips around the mouthpiece tightly and fully inhale. You will see the lights on the bottom of the screen turn orange.
   E. Slowly exhale into the mouth piece. The needle should move into the green section on the screen, you must try and keep the needle in the green section. If the needle is outside of the green section you are either blowing too hard or not enough. You will hear audio signals to help you maintain the correct pressure. A loud bleep will signal that you are applying too much pressure and a very low bleep will indicate that the pressure isn't strong enough.

Continuous sound indicates correct pressure and the needle will be in the green area

F. Your result will then display on the screen and please take note of this figure in your FeNo log.
G. Turn off machine

6. Participant Education - How to use your inhaler

In this study there is a small device attached to your inhaler; each time you take your inhaler the device will record your inhalation.

Below are instructions on how to take your diskus inhaler. The small device on top of your inhaler does not change the way in which you should take your inhaler and when you finish the study you should continue to follow these guides. As long as you are using a diskus inhaler then keep following the instructions below.

Study

- You will take the flixotide diskus inhaler for one week only (Visit 1)
- In the following visits you will be prescribed both Seretide and Ventolin diskus inhalers

Taking your inhaler

Find a quiet area, bathroom a good idea as you can look in the mirror so you can see yourself taking your inhaler. You have seen the nurse so this is a visual aid for you.

It is very important to stand up when taking your inhaler.

1. Open the inhaler until you hear a click.

2. Push the dispensing lever all the way back, Do not fiddle with this lever once it has been pushed back, this activates the medication by peeling back the foil that holds the powder, something like a cap-gun.

3. Hold your inhaler level away from your mouth. Blow out your mouth until all the air is gone from your lungs, should make a noise when you are doing this, this takes a few seconds (longer than you think).

REMEMBER

Do not breathe or blow into your inhaler!

4. When your lungs are empty, and you're dying for a breath, place the mouthpiece between your lips and take **a deep breath in,** remove the mouth piece from your lips.

5. Hold your breath and count to ten on your fingers, not in your head, (this slows you down) breathe out once you have counted to ten
6. Close the inhaler by using the thumb grip; do not fiddle with the dispensing lever, as this can dispense medication unnecessarily.

7. Gargle with water after you have used your inhaler, water will do, no need for mouth wash, this is another reason to take your inhaler in your bathroom.

Points of note/education for the Participant

You should not taste or feel the powder in your mouth, if you do; this is a sign that you are not taking it correctly. This can cause thrush. You are probably not emptying your lungs enough.

You are not eating, you are inhaling.

Good idea to check the mouth-piece occasionally for any accumulation of white powder, this might mean that you are not getting the medication and not taking your inhaler correctly. Take your ventolin when you feel is necessary and try to use the steps above as a guide. Take your seretide/fluticasone 12 hourly and follow the guide above.

Tips to remember to take your inhaler

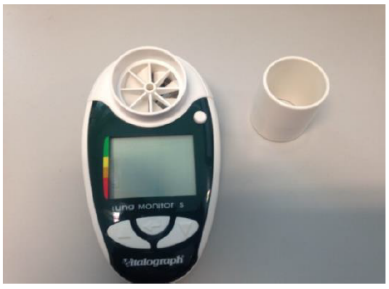
That Seretide/Fluticasone is a medication that works best if it is taken twelve hourly or as near to the twelve hours as you can make it. It is very important that you do not miss/skip your prescribed inhaler doses and that you take it EVERYDAY.

- Do you watch a programme at the same time every night?
- Can you set a reminder on your phone or set an alarm?
- Make it the first thing you do in the morning, start a routine!

5. Participant Education - How to use your electronic peak flow meter

How to take your peak flow?

1. Connect the mouthpiece into the device.

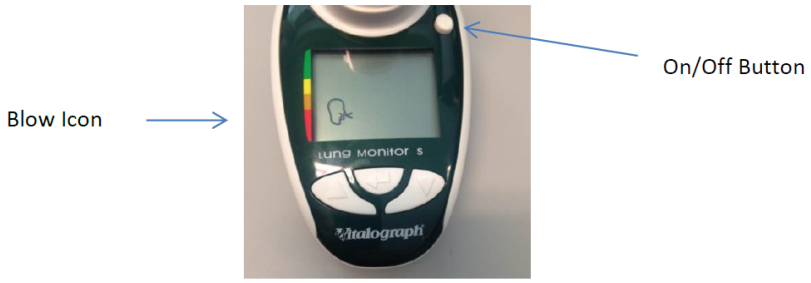


2. Turn the device on, (press ⏻) and wait for the blow icon

3. Take a deep breath in, hold your breath, seal lips tightly around the mouthpiece and blow out as hard as possible.

4. A PEF will be displayed on the screen following each blow.

5. Repeat twice Wait to see the blow icon before commencing each time.



6. To **turn off** press the on/off button. The device will switch off itself after prolonged inactivity.

7. Inhaler Record sheet

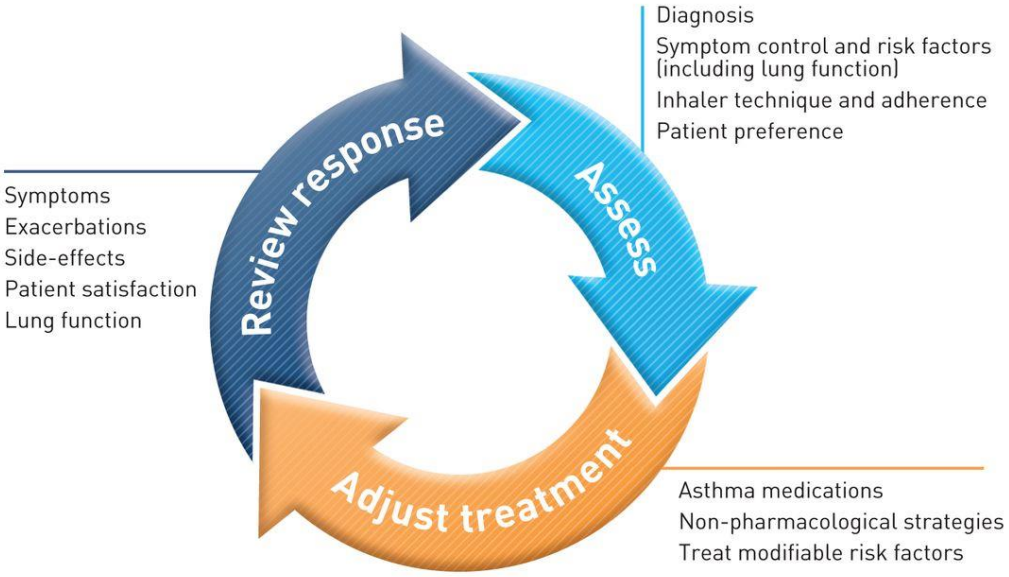
Only complete if you use a different Seretide or Ventolin inhaler without the INCA device during the study.

***** Please note, during the study you should only use the Seretide and Ventolin Inhalers with the INCA device attached*****

Inhaler Type (Seretide / Ventolin)	Date Used

Appendix 10: Global Initiative for Asthma (GINA) asthma management cycle to prevent exacerbations and control symptoms

The GINA cycle of asthma care



Good communication is essential – establish a partnership with the patient

- Consider health literacy, personal goals and fears, and cultural issues

Treatment choices

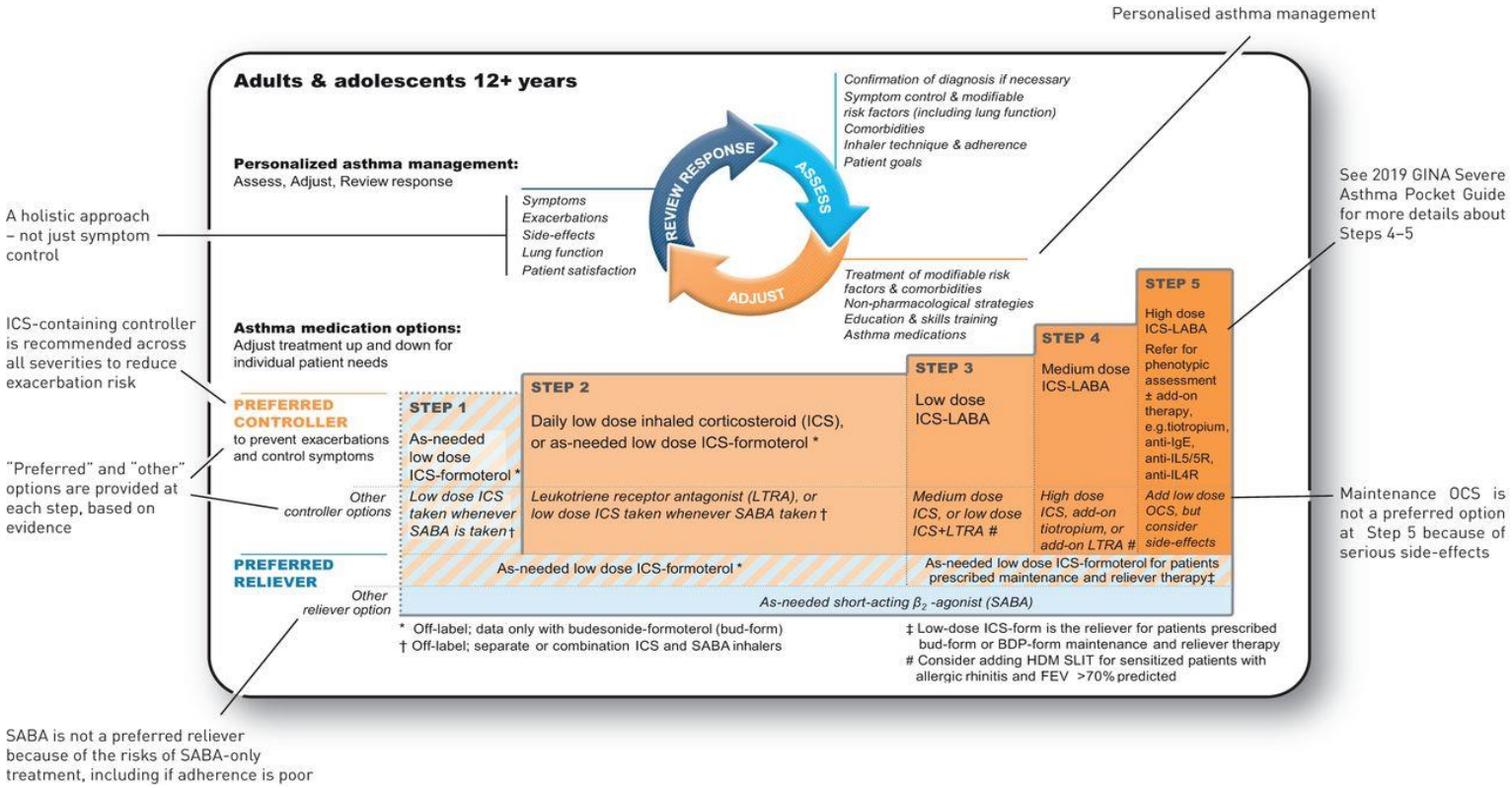
- *Population-level decisions:* efficacy, effectiveness, safety, cost, regulations
- *Patient-level decisions for tailoring treatment:* also discuss patient characteristics (phenotype) that predict response or risk; patient preference; practical issues inhaler technique, adherence, and cost; treat modifiable risk factors; use non-pharmacological strategies where appropriate

Stepwise medication adjustment

- *Consider stepping up* if uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique, adherence and modifiable risk factors first
- *Consider stepping down* if symptoms controlled for 3 months and low risk for exacerbations. For adults, ceasing ICS is not advised.

Written asthma action plan for all patients

Appendix 11: GINA asthma treatment strategy



Appendix 12: INCA SUN data analysis – STATA CODE

INCA SUN DATA ANALYSIS- STATA CODE

```
/*********************************************/
/*************IMPORT DATA*********************/
/*********************************************/
import excel "C:\Users\matshedisomokoka\Desktop\inca sun thesis data 21318 (002).xlsx",
sheet("incasun_thesis_data") firstrow case(lower)


/*********************************************/
/******DESCRIPTIVE STATS TABLE 1*************/
/*********************************************/
*Total number of participant in each group
tabulate randomisationcode

*Label groups
label define Group 0 "INCA biofeedback group" 1 "Control"
label values randomisationcode Group


*Age and BMI
tabstat age bmi, by (randomisationcode) stat(me sd n) long format

*Gender and Smoking (1= never, 2=ex-smoker, 3=current)
by randomisationcode, sort : tabulate gender
by randomisationcode, sort : tabulate smokingstatus

*Baseline FEV in L, FEV % predicted, FEV1/FVC ratio, PEFR in (L/min), FeNO.
label variable prefev1 "Baseline FEV1 (L)"
label variable prefev1percentage "FEV % predicted"
label variable prefev1fvcratio "FEV1/FVC ratio"
label variable v1pefr "PEFR(L/min)"
label variable v1feno "FeNO"
tabstat prefev1 prefev1percentage prefev1fvcratio v1pefr v1feno,by (randomisationcode)
statistics (me sd n) long format

*Serum eosinophils
generate serumeos = 1
replace serumeos = 0 if v1eosinophilcount<0.4
replace serumeos = . if v1eosinophilcount==.
by randomisationcode, sort :tabulate serumeos

*Oral steroid courses in the past year, Exacerbations in the past year
label variable pastyearsteroiduse "Steriods_PastYear"
label variable pastyearasthmaexacerbations "Exacerbations_PastYear"
```

```
tabstat pastyearsteroiduse pastyearasthmaexacerbations, by (randomisationcode) statistics
(me sd n)  long format

*Salmeterol/fluticasone dose % patients
replace v1seretidedose = "Seretide 500" if v1seretidedose == "Seretide 500mcg"
replace v1seretidedose = "Seretide 250" if v1seretidedose == "Seretide 250mcg"
replace v1seretidedose = "Seretide 250" if v1seretidedose == "seretide 250mcg"
by randomisationcode, sort :tabulate v1seretidedose


*ACT, AQLQ, EQ5D3L
tabstat v1act v1aqlq v1eq5d3l, by (randomisationcode) statistics (me sd n)  long format



/*********************************************/
/**TESTS - TECHNICALLY SHOULD NOT BE DONE FOR BASELINE CHARACTERISTICS*****/
/*********************************************/

ttest age, by(randomisationcode)
ttest bmi, by(randomisationcode)
prtest gender, by(randomisationcode)
tabulate smokingstatus randomisationcode, chi2
ttest prefev1, by(randomisationcode)
ttest prefev1percentage, by(randomisationcode)
ttest prefev1fvcratio, by(randomisationcode)
ttest v1pefr, by(randomisationcode)
ttest v1feno, by(randomisationcode)
prtest serumeos, by(randomisationcode)
ttest pastyearsteroiduse, by(randomisationcode)
ttest pastyearasthmaexacerbations, by(randomisationcode)
tabulate v1seretidedose randomisationcode, chi2
prtest v1seretidedose, by(randomisationcode)
ttest v1act, by(randomisationcode)
ttest v1aqlq, by(randomisationcode)
ttest v1eq5d3l, by(randomisationcode)


/*********************************************/
/******PRIMARY OUTCOMES - ANALYSIS***********/
/**********INTENTION-TO-TREAT*****************/
/*********************************************/

*Imputation -
        ******Does imputation need to be done?
        ******What variables need to be imputed?
        mi set wide
```

```
        mi misstable summarize
        mi register imputed /*Insert variable for imputation here*/
        mi impute regress /*Insert variable for imputation  and variables to be used in
imputing this variable here */, add(100)
        *Example:
        *mi impute regress Adherence Age Weight Smoker, add(100)
        *The above line imputes Adherence based on age, weight and whether the person
was a smoker or not. add(100) creates 100 imputations
        *Final model:
        mi estimate: regress Adherence feno site i.randomisationcode


*PO1: Mean rate of adherence over the last 12 weeks of the study calculated from the
*INCATM device,(2-4).

        *Actual adherence over last 12 weeks
        by randomisationcode, sort : summarize meanactualm678
        *Add site to model when multiple sites being analysed
        regress meanactualm678 v1feno ib1.randomisationcode

        *Attempted adherence over last 12 weeks
        by randomisationcode, sort : summarize meanattemptedm678
        *Add site to model when multiple sites being analysed
        regress meanattemptedm678 v1feno ib1.randomisationcode

*PO2: Proportion of necessary step up therapy prescriptions, calculated by looking at the
INCA
*device data and determining whether the step-up therapy was necessary.
        *m8actualauc>80 and v6act>19 patients are fine no step-up necessary (well
controlled no further therapy)
        *m8actualauc>80 and v6act<=19 step-up necessary for these patients
        *m8actualauc<80 and v6act<=19 patients are uncontrolled and adherence needs
assessment, not step-up therapy
        *Techincally should not occur but check: m8actualauc<80 and v6act>19

        generate stepup = 0 /*0 not necessary, 1 necessary*/
        replace stepup = 1 if m8actualauc>80 & v6act<=19
        replace stepup = . if m8actualauc==. | v6act==.
        by randomisationcode, sort :tab stepup
        *if values missing, you previously month's data (i.e. use m7actualauc for
m8actualauc)
        replace stepup = 1 if stepup==. & m7actualauc>80 & v6act<=19
        replace stepup = 0 if stepup==. & m7actualauc>80 & v6act>19
        replace stepup = 0 if stepup==. & m7actualauc<80 & v6act<19
        by randomisationcode, sort :tab stepup

        generate referral = 0
```

```
        mi misstable summarize
        mi register imputed /*Insert variable for imputation here*/
        mi impute regress /*Insert variable for imputation  and variables to be used in
imputing this variable here */, add(100)
        *Example:
        *mi impute regress Adherence Age Weight Smoker, add(100)
        *The above line imputes Adherence based on age, weight and whether the person
was a smoker or not. add(100) creates 100 imputations
        *Final model:
        mi estimate: regress Adherence feno site i.randomisationcode


*PO1: Mean rate of adherence over the last 12 weeks of the study calculated from the
*INCATM device,(2-4).

        *Actual adherence over last 12 weeks
        by randomisationcode, sort : summarize meanactualm678
        *Add site to model when multiple sites being analysed
        regress meanactualm678 v1feno ib1.randomisationcode

        *Attempted adherence over last 12 weeks
        by randomisationcode, sort : summarize meanattemptedm678
        *Add site to model when multiple sites being analysed
        regress meanattemptedm678 v1feno ib1.randomisationcode

*PO2: Proportion of necessary step up therapy prescriptions, calculated by looking at the
INCA
*device data and determining whether the step-up therapy was necessary.
        *m8actualauc>80 and v6act>19 patients are fine no step-up necessary (well
controlled no further therapy)
        *m8actualauc>80 and v6act<=19 step-up necessary for these patients
        *m8actualauc<80 and v6act<=19 patients are uncontrolled and adherence needs
assessment, not step-up therapy
        *Techincally should not occur but check: m8actualauc<80 and v6act>19

        generate stepup = 0 /*0 not necessary, 1 necessary*/
        replace stepup = 1 if m8actualauc>80 & v6act<=19
        replace stepup = . if m8actualauc==. | v6act==.
        by randomisationcode, sort :tab stepup
        *if values missing, you previously month's data (i.e. use m7actualauc for
m8actualauc)
        replace stepup = 1 if stepup==. & m7actualauc>80 & v6act<=19
        replace stepup = 0 if stepup==. & m7actualauc>80 & v6act>19
        replace stepup = 0 if stepup==. & m7actualauc<80 & v6act<19
        by randomisationcode, sort :tab stepup

        generate referral = 0
```

```
        replace referral = 1 if v6managementreferral==3
        replace referral = 1 if v6managementreferral==4
        replace referral = 1 if v6managementreferral==5
        replace referral = 1 if v6managementreferral==6

*Referral: Step-up therapy prescription = 1; No step-up therapy = 0
*Step-up: Based on INCA, step-up therapy prescription was needed = 1;
                *No step-up therapy was needed = 0

        tabulate referral stepup, chi2 exact
        by randomisationcode, sort :tabulate referral stepup

        *Step-up therapy decision appropriate or not, that is,
        *those that did not need stepup and did not recieve = correct decision
        *those that did need stepup and did recieve step-up = correct decision
        *those that did not need stepup and recieved step up = incorrect decision
        *those that did need stepup and did not recieve step-up = incorrect decision

        generate appropriatestep = 0
        replace appropriatestep = 1 if stepup == 1 & referral==1
        replace appropriatestep = 1 if stepup == 0 & referral==0
        tabulate appropriatestep randomisationcode, col chi2 exact

/*********************************************/
/******SECONDARY OUTCOMES - ANALYSIS**********/
/**********INTENTION-TO-TREAT*****************/
/*********************************************/
*Patient reported outcomes

*1. To compare the Asthma Control Test (ACT), Asthma Quality of Life Questionnaire
*(AQLQ) scores, EQ-5D-3L scores, Work Productivity and Activity Impairment-
*Asthma (WPAI-Asthma) scores and PEFR rates between the active and control groups.

*Asthma Control Test (ACT)
regress v6act v1feno site ib1.randomisationcode
*Asthma Quality of Life Questionnaire *(AQLQ) scores
regress v6aqlq v1feno site ib1.randomisationcode
*EQ-5D-3L scores
regress v6eq5d3l v1feno site ib1.randomisationcode
*Work Productivity and Activity Impairment-Asthma (WPAI-Asthma)
regress v6wpaiq1 v1feno site ib1.randomisationcode
regress v6wpaiq2 v1feno site ib1.randomisationcode
regress v6wpaiq3 v1feno site ib1.randomisationcode
regress v6wpaiq4 v1feno site ib1.randomisationcode
regress v6wpaiq5 v1feno site ib1.randomisationcode
regress v6wpaiq6 v1feno site ib1.randomisationcode
*PEFR rates
```

```
regress v6pefr v1feno site ib1.randomisationcode

*Clinical outcomes

*2. To examine and compare the proportion of patients reaching stated clinical goals.

*3. To compare the proportion of patients who are refractory, defined as having actual
*adherence =80%, =1 exacerbations, PEFR am/pm <80% and ACT =19.

*4. To compare the proportion of patients who are non-adherent and remain uncontrolled,
*i.e. Actual Adherence <80%, PEFR am/pm <80% and ACT=19.

*5. To compare the time to first exacerbation (defined by =20% fall in PEFR and at least
*doubling of reliever use for 3 consecutive days or prescribed rescue oral steroid)
*between the active and control groups.

*6. To compare the proportion of patients with inhaler related side effects including oral
*candidiasis between the active and control groups.

*7. To compare changes in blood eosinophil,Äôs, periostin and Fractional Exhaled Nitric
*Oxide (FeNO) between the active and control groups.

*8. To investigate the relationship of biomarker changes in relation to adherence.

*9. To compare the proportion of patients who were clinically stabile (i.e. proportion of
*patients who required no daily reliever use in the month prior to study end) between
*the active and control groups.

*10. To investigate the relationship between changes in FeNO (characterised into
*FeNo>45ppb Or FeNO<45ppb) and adherence.

*11. To investigate the relationship between 7-day FeNO suppression and clinical and
*biomarker outcomes.




/*******************************************/
/******PRIMARY OUTCOMES - ANALYSIS***********/
/**********PER PROTOCOL >80%****************/
/*******************************************/

*delete those who did not adhere to protocol.
*patients need to adhere >80%
*once patients are deleted, repeat all analysis above.
```

```
/*******************************************/
/******SECONDARY OUTCOMES - ANALYSIS**********/
/**********PER PROTOCOL >80%*****************/
/*******************************************/

*delete those who did not adhere to protocol.
*patients need to adhere >80%
*once patients are deleted, repeat all analysis above.



/*******************************************/
/************ADDITIONAL ANALYSIS************/
/*******************************************/

*If any of the variables at baseline showed a difference between groups
*the above models (ITT AND PP) must be run including the variables showing a
*marked difference at baseline
```