

Investigating the factors affecting adherence to inhaled corticosteroids in patients with asthma using primary care data in the UK

Amelia C Taylor BSc (Hons)

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Abstract

Background: Poor adherence to inhaled corticosteroids (ICS) is known as the main cause for therapeutic failure in asthma treatment and associated morbidity. Adherence is complex and can have many causes, which will vary between conditions, treatments and patients. To improve adherence, it is vital to understand what effects a patients adherence, so appropriate interventions can be developed and targeted, both for the patients who would benefit most and at the most important points in treatment. Very few studies have characterised the variables associated with poor adherence and how these differences may change over time, and the most appropriate methodology for investigating this relations have not previously been defined.

Aims and objectives: The aim of the PhD study was to investigate what characteristics associated with a patient's adherence to ICS, and to investigate whether these relationships change over time using a large primary care dataset. The objectives included the development of a longitudinal measure of asthma patients' adherence to ICS, then to investigate the time dependent relationship between adherence and other available patient variables by trialling a number of different methods. In addition, the effect of adherence on clinical outcome in asthma was tested, since counter intuitively many studies have not previously found a clear relationship between the variables.

Methods: A retrospective longitudinal study using a large cohort was conducted using primary care data from the Clinical Practice Research Datalink (with Hospital Episodes Statistics data) between 1997 and 2010. Asthma patients aged between 12

and 65 years, without a diagnosis of chronic obstructive pulmonary disease were included in the study cohort. ICS prescriptions were extracted and used to calculate the annual prescription possession ratio (PPR). Several definitions of the PPR measure were tested to develop a proxy measure to represent adherence. Variables related to clinical outcomes and other characteristics were also identified for each patient in the cohort. A two-way analysis was conducted to compare the relationship between adherence and each patient variable with time, and then four methods were used to further investigate the relationship between adherence and patient exacerbations including; (1) comparing adherence in the year before and after an exacerbation; (2) descriptively exploring the clinical outcomes associated with different adherence levels; (3) identifying the relative risk of an exacerbation associated with adherence defined by different cut off levels of PPR; and (4) descriptively exploring the effect of adherence on outcome and outcome on adherence over time. Finally, the available variables associated with adherence (including previous adherence and clinical outcomes) were analysed in a dynamic panel model to understand explore the effect of variables on patients' adherence to ICS which allows for the feedback effects of previous adherence and clinical outcome and the effect of time on adherence.

Results: Many patient variables were found to effect adherence. When modelling the effect of patient variables on adherence, adherence was found to be lower in younger patients (+0.11%/year), patients with fewer years in the study (+0.25%/year), with more severe asthma (step 5 patients had a 3.32% lower PPR than step 2 patients), with good control (5.21% lower), with lower previous

adherence (-0.51% per % PPR), and who had not previously experienced an exacerbation (0.87% lower compared with patients who had experienced no primary car exacerbation and 1.45% lower for those who experienced no secondary care exacerbation).

Adherence increased with patient year, consistently across most subgroups, with the following exceptions; the 20-25 year old age group had lower initial adherence (53.9%) than the younger patients (58.3%), patients registered in the East Midlands had the lowest adherence (57.7%), but increased over time to become the highest (90.7%) and in the first year of the study the adherence for patients treated at step 2 of the guidelines was the lowest (57.5%) but it increased over time to become the second highest step (85.7%).

Conclusion: This longitudinal follow-up study using electronic patient records over time was useful to identify the effect of multiple patient variables on adherence. The main characteristics associated with poor adherence were the characteristics that we would associate with better health, or less severe asthma. Therefore, the interventions to improve adherence or to review the appropriateness of treatment should be developed to target younger patients, early on in treatment before they have experienced an exacerbation of their asthma symptoms.

The PPR measure developed was useful to measure changes in adherence over time, as a measure of the maximum amount of medicine that the patient had available to them, expressed as a percentage of their recorded prescribed dose. However there are some important limitations to the PPR measure including most importantly that adherence must be measured against a routinely prescribed daily

dose of ICS and medicine prescribing and not medicine taking is measured, meaning that adherence is likely to be overestimated.

The methods used to analyse the adherence measure had not previously been used to assess adherence in asthma. By using the results from each analysis method, information about different parts of the relationship between adherence and other patient variables including their exacerbation risk and time could be combined, which uniquely allowed the longitudinal measurement and analysis of adherence in asthma over extended study duration.

Publications

Peer reviewed paper (Appendix 23)

Taylor A, Chen LC, Smith MD. Adherence to inhaled corticosteroids by asthmatic patients: measurement and modelling. International journal of clinical pharmacy 2014; 36: 112-9.

Conference presentations

Taylor A, Chen LC, Smith MD. Adherence to anti-asthmatic inhaled corticosteroids: measurement for the UK. Poster presentation, Royal Pharmaceutical Society annual conference 2013, "Research Posters." International Journal of Pharmacy Practice **21**: 30-137.

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List of abbreviations

AQLQ	Asthma quality of life questionnaire
BMI	Body mass index
BNF	British National Formulary
BTS	British Thoracic Society
CCI	Charlson Comorbidity Index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
DH	Department of Health
DPI	Dry powder inhaler
GINA	Global Initiative for Asthma
GP	General Practitioner
GPRD	The General Practice Research Database
HES	Hospital Episode Statistics
ICD-10	International Classification of Diseases-tenth revision
IMD	Index of Multiple Deprivation
IQR	Interquartile range
ISAC	Independent Scientific Advisory Committee
LABA	Long acting beta agonist
LSOA	Lower super output area
MDI	Metered dose inhaler
MHRA	Medicines and Healthcare Products Regulatory Agency
MPR	Medicine possession ratio
NAEPP	National asthma education and prevention programme
NCCSDO	Nation coordinating centre for service delivery and organisation
NDD	Numerical daily dose
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OA	Output area
OCS	Oral corticosteroid
OPCS	Office of Population Census and Surveys
PDC	Proportion of days covered
PPR	Prescription possession ratio
QOF	Quality and Outcomes Framework
RCP	Royal College of Physicians
RCT	Randomised control trial
SABA	Short acting beta agonist
SIGN	Scottish Intercollegiate Guidelines Network
UK	United Kingdom
VAMP	Value Added Medical Products
WHO	World Health Organization

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Chapter 1 Introduction

1.1 Medicine adherence in patients with asthma

Asthma is a highly prevalent chronic disease; characterised by symptoms including wheezing; a shortness of breath; a tight chest and coughing. These symptoms can vary, often occurring in response to exposure to a trigger such as an allergen or to exercise. [1]

It has been reported that 5.4 million people in the United Kingdom (UK) received treatment for asthma in 2014 and 4.3 million of those were adults. [2] Despite effective treatments and evidence based guidelines for the treatment of asthma being available, [3] the outcomes for asthma patients are suboptimal and consequentially the disease burden to the National Health Service (NHS) is high. From 2000 to 2011 there were approximately 1000 to 1200 asthma related deaths per year reported in the UK. [4] The UK and Australasia have the highest prevalence of asthma in the world, with the USA and parts of South America also having high prevalence. [5 6] In 2011/2012, in the UK there were 65,316 asthma related hospital admissions (40,243 in adults). [7] It has been estimated that improved care could prevent 90% of deaths and 75% of hospital admissions associated with asthma. [2 8]

Pharmacotherapy is still the mainstay of asthma treatment. The goal of asthma treatment is to reach complete control of the disease. Amongst other asthma medicines, a routine daily use of inhaled corticosteroids (ICS) is recommended for most asthma patients. The efficacy of ICS is supported by robust clinical evidence and has been recommended within clinical guidelines for the treatment of asthma. [3] However, it is often reported that asthma patients often do not follow this

recommendation by not adhering to ICS, reported to be the main cause for poor asthma control [1 7 9 10] and its associated morbidity. In addition, a review of the efficacy of interventions for improving adherence to ICS was also found to be suboptimal. [11]

Since asthma is a chronic condition requiring adherence to long-term treatment, the development of interventions for improving patients' adherence to medicines relies on a good understanding of factors associated with poor adherence [1] and whether the effect of these factors are stable over time.

A knowledge gap in our understanding of the causes of poor adherence in asthma and how these factors and adherence interact over time was highlighted by the Horne *et al*. in 2005. [1] Pando *et al*. (2010) also suggested that a study to identify the determinants associated with suboptimal prescribing of ICS would be interesting to understand the gaps between treatment goals, asthma control and for the planning of interventions. [12] This knowledge could help to identify specific "at-risk" groups of patients to be targeted for interventions [13] at the most appropriate points in their treatment, and also to aid the development of specific interventions to target the root cause of the low adherence to appropriate prescriptions.

1.2 Temporal effects of factors influencing adherence in asthma patients

The majority of previous studies which investigated adherence to ICS in asthma patients and the factors associated with adherence, were generally cross-sectional or short-term cohort studies [1 14] in relatively small populations, and often conducted in a clinical trial setting rather than in routine clinical practice. These

studies were neither able to evaluate the combined effect of multiple different characteristics on adherence, or to assess changes in the effect of these variables on adherence over the course of treatment. Clinical trials also often exclude patients with certain characteristics such as comorbidities or if they smoke, making it impossible to understand the differences in adherence between these patients, [15] so may not be representative of a normal asthma population.

In addition, none of the previous studies investigated how the relationships between multiple patient variables and adherence changes over an extended period of time. A systematic review of studies measuring asthma inhaler adherence using observational data by Dima *et al*. in 2014 [14] identified only two studies that considered repeated measures of adherence which are important to determine casual influences of adherence; this PhD study, [16] and a study from the USA looking at medicine beliefs. [17]

Because of the short term nature of most previous studies, the temporal effect of patient characteristics on adherence and the effect of previous adherence on future adherence are not well understood. These factors are particularly important in evaluating treatment effectiveness of any long-term condition. As adherence could change over time, and hence any intervention needed to improve adherence, may also need to be personalised over time.

1.3 The complex relationship between adherence to ICS and outcome of asthma control

It is generally believed that an improvement in adherence is expected to lead to an improvement in clinical outcome, as stated by the former US Surgeon General, C

Everett Koop (1985) that “drugs do not work in patients who do not take them”. Under this assumption, many adherence studies in asthma did not evaluate the effect of adherence on clinical outcome; however, some studies have not found a significant effect of adherence to ICS on asthma exacerbations. [18] This may be caused by different levels of adherence required between individual asthma patients to achieve control. There are a variety of factors that may influence (or confound) this causal relationship between adherence to ICS and asthma control, such as the patients asthma severity, the patients beliefs or the patients understanding of their asthma. The relationship between adherence and clinical outcome is further complicated by confounding factors that may also change over the course of a patient’s treatment such as the effect of patient adherence on asthma control. Differences between the methods used may also affect his relationship such as how the clinical outcome was measured, by exacerbation occurrence or by asthma control or symptoms.

Therefore, adherence to ICS in patients with asthma is not a simple one-way causal relationship with a single clinical outcome; instead there is a complex relationship between adherence, exacerbations, patient asthma severity and other patient’s characteristics. So far, this relationship is poorly understood, especially how these measures may change over the course of treatment.

Randomised controlled trials have previously been used to study adherence, but to study medicine use over an extended period of time makes this type of study prohibitively expensive, especially when a large study cohort is required to investigate the association between multiple patient characteristics on adherence.

The availability of primary care data in the UK with linkage to secondary care data provides a rich source of data that can potentially be used to study the long-term relationships between patient's characteristics and adherence to medicines. Since very few studies have investigated this type of temporal relationship between adherence and other patient characteristics in asthma, especially over an extended period of time, the methodology required has not previously been established.

1.4 Aims and objectives

The aim of the PhD study is to identify patient variables associated with an asthma patient's adherence to ICS, and to investigate the temporal relationship between adherence and those variables; the objectives included:

1. To use an appropriate data set to develop a repeated measure of adherence and other study variables over time
2. To identify the patient variables and to explore the potential (temporal) relationship with adherence over time
3. To model the effect of the patient variables (covariates) on adherence over time
4. To understand and quantify the effect of adherence on outcome

1.5 Research strategy

A comprehensive literature review (Chapter 2) was first conducted to understand the characteristics and treatments for asthma, adherence in general and the importance of patient adherence in asthma. In addition, literature relating to the methods used to measure adherence were reviewed, focusing on the use of large retrospective databases for long-term studies and of asthma studies found to have

used these methods. A review of the literature was conducted to summarise our current understanding about the causes of low adherence and outcomes in asthma, especially in the UK health system and to identify the gaps and inconsistencies in evidence currently available.

In this PhD study, an observational design was used, using a longitudinal dataset to conduct a cohort study (defined in Chapter 3). The patient variables were identified from the cohort data and characterised (Chapter 3).

A proxy measure of ICS adherence, the prescription possession ratio (PPR), was then developed using the prescribing data for the study cohort in a panel data structure. Several definitions of the PPR measure were tested to identify the most 'suitable' definition for the PPR measure as the proxy to represent adherence to ICS (Chapter 4).

Similarly to Chapter 4, where the adherence measure was derived, in Chapter 5 the patient variables to measures asthma exacerbation occurrence, severity and control (identified in Chapter 2) were also identified from the cohort's GP records in panel data format. The derived severity, control and exacerbation data were compared to understand the relationship between these variables (Chapter 5).

Once the cohort and the variables for the study were prepared, they could be analysed.

Different methods of analysis were trialled to investigate different aspects of this complex relationship between adherence, clinical outcome and the other patient characteristics and how these relationships may change over time:

- A two-way analysis was conducted to observe any differences in mean adherence and when sub grouped by patient variable (derived in Chapters 3 and 5) with time (Chapter 6).
- To investigate the relationship between clinical outcome and adherence four methods were used; (1) adherence in the year before and after an exacerbation were compared; (2) the clinical outcomes associated with different adherence levels were explored descriptively; (3) the relative risk of an exacerbation associated with adherence defined by different cut off levels of PPR was calculated and compared; and (4) the effect of adherence on outcome and outcome on adherence over time was explored descriptively (Chapter 7).
- Finally, all variables associated with adherence (including previous adherence and clinical outcomes) were analysed in a dynamic panel model to understand and explore the effect of variables on patients' adherence to ICS whilst controlling for the combined effects of the other variables including time. This model also allowed for the feedback effects of previous adherence and clinical outcome and the effect of time on adherence (Chapter 8).

Combining the results from the analysis methods, information about different parts of the relationship between adherence and other patient characteristics including their exacerbation risk and time, uniquely allowed the longitudinal effects on adherence to ICS to be studied in asthma over extended study duration. These combined results and their clinical relevance are discussed in Chapter 9.

Chapter 2 Literature review

In this chapter the available literature was reviewed to understand the condition of asthma and how it is treated, and patient adherence to medicines in the treatment of asthma. The current evidence about the causes of low adherence and outcomes in asthma, especially in the UK health system were summarised and the gaps and inconsistencies in evidence currently available were identified.

One of the important causes of poor outcome in asthma patients was adherence; therefore, information about general adherence, adherence in asthma patients and variables that may affect adherence in asthma including the effect of time was investigated further, where evidence was already available.

The methods that had previously been used to measure adherence in previous studies were then researched to identify the methods that could be used in this study. Asthma adherence studies that used large retrospective databases were then reviewed with a special focus on the methods that were used to measure adherence in any long-term studies conducted.

2.1 Epidemiology and the disease burden of asthma

Asthma is a chronic respiratory disease, caused by constriction of the airway smooth muscle (bronchoconstriction) due to a chronic inflammatory process which is triggered by various stimuli such as viral respiratory infections, exercise, smoke, cold, and allergens e.g. pollen, animal fur and house dust mite. The etiology of asthma is unknown, but it is thought to involve both genetic and environmental factors. Some genetic variants may only cause asthma when they are combined with specific environmental exposures. [19]

The diagnosis of asthma is based on the presence of two or more of the symptoms including wheeze, breathlessness, chest tightness and cough, plus the presence of variable airway obstruction (measured using spirometry) and no alternative explanation for those symptoms. [3] The presentation of signs and symptoms in patients with asthma varies,[20] some patients present daily symptoms but characterised by episodes known as exacerbations - a worsening of symptoms. Exacerbations can vary in frequency and severity, but severe exacerbations can be life threatening. These symptoms of asthma may prevent normal work, and may limit domestic and social activities. [21]

Asthma may start at any age but usually develops in childhood. A confirmed diagnosis of asthma is difficult until a clinical pattern is established. [22] In children, a specific diagnosis of asthma is less reliable than in adults since in pre-school children and infants, episodes of wheezing, cough and difficulty breathing are often associated with respiratory infections, with no persisting symptoms. [23] Therefore, many patients who are diagnosed with asthma in childhood, especially those diagnosed before two years of age become asymptomatic by mid-childhood [3], at puberty [24], or by school age [3], especially patients with mild or moderate asthma. [24]

The Global Initiative for Asthma (GINA) classify asthma as intermediate, mild, moderate or severe, based on the severity of the patient's asthma characteristics if they were not receiving any treatment (Appendix 3). [25]

The prevalence of asthma worldwide varies between 1% to 18%, [20] it is estimated in 2004 that 300 million people of all ages are affected by asthma globally. [20 26 27] A commonly quoted figure from 2001 estimated asthma prevalence to range from

12.5% to 15.5% in the UK. [21] However, more recently a large study using multiple national data sets and surveys in 2011/2012 estimated the prevalence of asthma to be 15.6%, consistent with the upper end of the range from the 2001 report. The 2001 study estimated that 5.1 million people were treated for asthma, of which 3.7 million were adults and 1.4 million were children. By 2007, the total number of people with asthma in the UK increased to 5.2 million, [21 28] and 5.4 million by 2010. [29 30] The study using 2011 data estimated that 6 million people had received treatment for asthma (prevalence of 9.6%).[31]

The prevalence of asthma varied by characteristics of the population, for example, according to the 2001 wave of the Health Survey for England, the prevalence of asthma in women (16%) was slightly higher than in men (13%) in England. [28] Other studies also reported that the prevalence of asthma was significantly different between patient with different socioeconomic status' [32] and race [33] where Hispanic or Black ethnic groups had higher asthma prevalence, was also likely to be associated with deprivation.

Poorly controlled asthma can cause a significant effect on the quality of life for the patient and their family. [28] In adolescence, asthma has been reported to be associated with an increased likelihood of major depression, panic attacks and anxiety disorder. [3] In 2004, the Global Initiative for Asthma (GINA) estimated that globally, 15 million disability adjusted life years are lost annually due to asthma. [27] Additionally, in 2001, the National Asthma Campaign reported that 18 million work days are lost due to asthma in the UK. [21] In 2003 this lost work was estimated to account for a loss in productivity of £1.2 billion. [8]

In 2004, annual asthma related deaths worldwide were estimated to be 250,000 people. [20 26 27] According to the National Institute for Health and Care Excellence (NICE) report in 2013, there were around 1000 deaths per year from asthma in the UK. [30] Asthma related death rates in the UK have shown little improvement in the last 20 years, despite medical advances and improvement in asthma management. [8]

Furthermore, asthma incurs a considerable disease burden on health care resources [1] in many Western countries. In 2001, the total cost of asthma treatment to the UK NHS was estimated to be £850 million [21] and it increased further to £1 billion in 2014. [2] In 2004, there was an estimated 4.1 million GP consultations in the UK for asthma each year. [8] In 2003, there were 59,859 hospital admissions in the UK for asthma, rising to 67,713 in 2004. [34] Only 11% of patients have the most severe asthma but have been found to account for 33% of the healthcare costs. [35] The National Asthma Campaign in 2007 and the Department of Health in 2011 both recorded that it has been predicted that three quarters of hospital admissions for emergency treatment for asthma could be avoided with appropriate care, saving an estimated £43.7 million annually, [34] however, the original source of this data is not recorded in either document.

2.2 Treatment strategies for the management of asthma

Guidelines for the management of asthma have been developed since the first global opinion-based asthma guidelines were developed in Australia and New Zealand in 1989. In the same year, the Global Initiative for Asthma (GINA), a collaboration of organisations who work together to reduce asthma prevalence, morbidity, and mortality, developed science-led recommendations for international asthma care

and management (most recently updated in 2016 [20]). In 1991, the National Asthma Education and Prevention Program (NAEPP) [36] in the United States of America published a set of guidelines for the diagnosis and management of asthma. Canada then developed its own evidence based guidelines in 1989, most recently updated in 2010. [37]

In the UK, asthma guidelines were first published in 1990 by the British Thoracic Society (BTS) [38 39], and separately by the Scottish Intercollegiate Guidelines Network (SIGN). [40] In 1999, BTS and SIGN agreed to produce a new joint asthma guideline. This was published in 2003 [41] and is updated regularly. This guideline used the SIGN methodology, developed by gathering evidence from literature dating from 1966. In the UK, the most recently updated guidelines for asthma were published in 2016 [3] jointly by the BTS and the SIGN, although, within this study the prescribing information from the 2014 guidance was used, since the stepwise approach used in this study, applicable to the prescribing guidance during the study period, was updated in the 2016 guidance update. Other major updates to the 2016 guidance included information and evidence added to support asthma diagnosis, combination inhalers, monoclonal antibodies, critical care, discharge planning in children and adherence. A table to categorise each inhaled corticosteroid drug substance by dose, has also been expanded.

In addition, the NICE Quality Standard for asthma [30] is also published to identify the high priority areas to ensure quality of asthma treatment, and Quality Outcomes Framework (QOF) [42] targets are used to incentivise improved patient care by GPs.

Since the first guideline was developed, the guidelines have taken a reasonably consistent approach to diagnosis and pharmacological management, [43] with the addition of new medicines and emerging evidence over time, used to develop the guidelines and to support best practice. In the UK, the QOF is used to incentivise good practice alongside the BTS/SIGN guidelines, meaning that the management of asthma is supported by efficacious treatments and evidence based management strategies, which if adhered to should lead to an improved patient outcome.

2.2.1 Pharmacotherapy of asthma

The British guidelines [3] advise two strategies to help patients to achieve good control of their asthma and to prevent asthma symptoms; the avoidance of asthma triggers (where appropriate) and the use of appropriate medicines. There are two types of medications commonly recommended in the asthma guidelines for the management of asthma. Medicines used to control asthma including anti-inflammatory drugs and bronchdilators (inhaled corticosteroids, oral long-acting β_2-agonists (LABA), xanthine derivatives, chromes (cromoglycate, nedocromil) and anti-IgE agent (omalizumab)), are often referred to as 'preventers' and recommended to be used regularly (daily) to control the disease inflammatory processes. [44] Medicines used for the treatment of asthma symptoms including inhaled short-acting β_2-agonist (SABA), ipratropium, β_2-agonist tablets or syrup, or theophyllines are often referred to as 'relievers'. They are designed to rapidly reverse bronchoconstriction and relieve symptoms, and are recommended to be used 'as needed' to treat acute exacerbations [44] (Appendix 1).

In the UK, both of these types of medicines must be prescribed by a health care professional, who is usually based in a primary care medical practice, or a specialist asthma clinic.

Since the first British guidelines published in 1990 [38], a 'stepwise' approach to the management of asthma has been recommended, and each treatment step is categorised by the medicines required to achieve asthma control (see Appendix 2). Treatment is initiated at the most appropriate step for the patient and when necessary medicines are added to the therapy regimen at each step increase to achieve control, and stepped back down when control is achieved. Therefore, the treatment step can be considered to be an indicator for the severity. Minor exacerbations of asthma symptoms may be treated by taking inhaled SABA's, although a short course of oral corticosteroids is often also needed, usually prescribed within primary care. [28] More severe exacerbations may require more complex treatment within secondary care, either within the emergency department or by inpatient admission. Therefore, the treatments required by the patient can indicate the severity of an asthma exacerbation.

2.2.2 Asthma control

The goal of asthma management, as defined within the British Guideline on the Management of Asthma (2016)[3] is:

"no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no asthma attacks, no limitations on activity including exercise, normal lung function (in practical terms forced expiratory volume (FEV^1) and/or peak

expiratory flow rate (PEF) greater than 80% predicted or best), and minimal side effects from medication."

Asthma control has been defined as the "degree in which the therapy goals are met" [45] or "to reach complete control of the disease". [3] Asthma patients at any level of severity can experience severe exacerbations of symptoms if they have poor control, which may require rescue medicines within primary or secondary care. In the most severe cases, an asthma exacerbation can lead to death, but in all cases would have a negative effect on the quality of life for the patient.

Several different methods for assessing a patient's asthma control within primary care are recommended in the British guidelines, [3] including:

(1) Lung function tests, including peak flow and spirometry.

(2) Questionnaires, including the Royal College of Physicians' (RCP) '3 questions', the Asthma Control Questionnaire or Asthma Control Test, or the Mini Asthma Quality of Life Questionnaire (AQLQ).

(3) Tests for sputum eosinophil count, airway responsiveness and exhaled nitric oxide, which provide information about future risk of exacerbation of symptoms.

For patients who are already treated for asthma, a secondary measure of asthma control could include measuring the use of rescue medication such as oral steroids, hospitalisation to treat an exacerbation of asthma, or the assessment of over use of reliever medicines such as SABA's as a ratio of ICS to SABA use. [46].

If a patient is found to have poor control, the British guideline recommends that patient's adherence to existing treatments; inhaler technique and triggers of exacerbations should be assessed before asthma treatment is stepped up. [3]

2.2.3 Factors influencing asthma control

A variety of factors have been reported to affect patients' asthma control in previous literature, including patient related factors (including demographic, lifestyle variables and socioeconomic status), the characteristics of asthma, therapy variables, the healthcare system where the patient was treated and importantly, adherence; these are described in the following sections.

2.2.4 Patient related variables

2.2.4.1 Demographics

A patient's gender, age and where they live (within the UK) have been previously found to influence asthma control.

A retrospective study using hospitalisation data from Canada and New Zealand in in 1995 to 1999, found that younger males, up to age 10 years experienced approximately twice as many exacerbations requiring hospital admission than females, but between age 20 to 60 years, females were found to experience two to three times as any exacerbations as males. [47 48] This trend, where males experienced a higher rate of asthma admissions than females was also observed in Review by Osman (2003), using Scottish hospital admission data. The author attributed "sociocultural influences on diagnostic labelling or sex differences in lung development and function" for the differences.[49]

In a study in France using pharmacy records and questionnaires, a higher proportion of patients aged 41-50 years old were found to have uncontrolled asthma than younger patients aged between 18 and 40 years. [50] In addition adult females were found to have poorer control than males. [50] A study from the UK, using hospital admission data between 1958 and 2003 [51] found that in 2003 the 0 to 4 year olds had the highest admission rates for asthma, followed by 5 to 14 year olds. The 15 to 44 year olds and patients over 45 years old had the lowest rates, but conversely death rates due to asthma were found to increase with age group.

Asthma UK, as part of a campaign about variations in hospital admissions for people with asthma, using 2004 HES data, reported that there were 80,593 emergency hospital admissions in the UK. The proportion of hospital admissions were found to be 76% higher for people who lived in the North-West England than for those who live in the East of England. [52] The North-East England (15% higher than the national average) and Wales (10% higher than the national average) also had higher than average admissions, compared with lower rates observed in the South of England. [52] No more recent or more comprehensively recorded studies were found to support this evidence.

2.2.4.2 Lifestyle and comorbidities

Whether a patient smokes, is pregnant or has any comorbidities, are also believed to influence asthma control.

There is evidence that smoking can reduce the efficacy of inhaled and oral corticosteroids used to control asthma, believed to be caused by corticosteroid insensitivity, [53 54] where a significantly greater increase in mean morning peak flow

measurements were observed in non-smokers than in smokers following patients taking inhaled corticosteroids. In a study comparing asthma control between groups of patients who reduced, abstained or continued smoking, found that asthma control (SABA use and ICS dose, symptoms and bronchial reactivity) was improved by stopping smoking compared with patients who still smoked. [55] The BTS/SIGN British asthma guidelines (2014 and 2016), report that direct or passive smoking adversely effects asthma control. [3 54 56] In a systematic review of longitudinal studies looking at the effect of parental smoking on wheezing and asthma in children, 13 studies were identified that considered the effect of passive smoking on asthma severity. The studies used a number of different measures of severity, but generally found that poorer asthma control was associated with the children with asthma who were exposed to passive smoking. [57]

Evidence for the the association between pregnancy and asthma exacerbation is still inconclusive. The British guidelines report evidence from a review of 14 studies that during pregnancy about one third of asthma patients experienced an improvement in their asthma, one third experienced a worsening of symptoms, and one third remained the same. [58] A systematic review by Murphy et al. (2006) concluded that the most likely causes for increase exacerbations during pregnancy were increased susceptibility to viral infections and discontinuation of anti-inflammatory medications. [59]

The British asthma guidelines advise that a "weight reduction in obese adults with asthma improves lung function"[3] and a study about the effect of weight on asthma control found that patients with a high body mass index (BMI) (an indicator for being overweight) had a higher risk of poor asthma control. [50] However, Cochrane review

of evidence about interventions for weight loss on measures on asthma control from RCT's, found that there was no good quality evidence to prove that interventions for weight loss were beneficial to improve asthma control, [60] and concluded that the benefit of weight loss for asthma control was uncertain due to the methodology quality of the studies.

Comorbidities including arthritis, stroke, heart disease and osteoporosis have been found to be more common in patients with asthma. Comorbidities such as osteoporosis may be caused by high steroid use, used to treat severe asthma, so may be a result of the patient having asthma. One study of coexistent conditions in asthma patients reported that comorbidities "tend to cluster together particularly in older people." Patient factors such as smoking status were believed to contribute to this higher rate of asthma and comorbidities such as cardiac disease, cerebrovascular disease. Alternatively asthma could be diagnosed due to breathing difficulties as a result of these conditions. [61]

2.2.5 Socioeconomic status related factors

The association between socioeconomic status and asthma control remains unclear, where some studies reported a non-significant association between asthma symptoms and deprivation, [62 63] but others reported poorer outcomes in the most deprived patients, where more deprived patients were more likely to be either admitted or readmitted to hospital and have worse health outcomes post discharge. [64 65] A number of different methods are available to measure SES, depending on the method chosen; this may affect the relationship between SES and asthma outcome. Measures may include financial, health, education, services or crime, either for

individuals, or where this is not available, aggregate measures using area data from a census or an administrative database can be used. Examples in the UK include the the Carstairs Index, [66] the Townsend Index [67] and the Index of material deprivation. [68] The Carstairs and the Townsend scores are based on UK census data and are based on a lower number of factors than the IMD score. [69] For example, both measures, unlike IMD, do not include access to services education or skills measures, which may influence health outcomes.

In a study in 2009, where 30 qualitative interviews were conducted on asthma patients, medication cost was found to affect some patients' by reducing 'preventer' medicine use, including ICSs. [70] This suggests that decisions about medicine management by the patient were affected by whether a patient had a prescription payment exemption, where the effect would be greater in patients who are more deprived.

2.2.6 Condition related factors

Patients condition characteristics including asthma control, the severity of asthma, whether the patient has previously experienced an exacerbation of their asthma symptoms or are likely to experience in the future, are all expected to be associated.

By definition, a patient is considered to have higher severity of asthma if they need a greater number and/ or dose of asthma medicines to try to establish good control. [3]

This relationship may not be clear in some patients with severe asthma, which is well controlled with medicines, since they may meet the same symptomatic criteria as patients with mild asthma, i.e. experience few exacerbations, but would require

higher doses of anti-inflammatory medicines than prescribed to patients with less severe asthma to achieve this control. [71] Other patients with severe asthma would have poor control of their asthma and would be at a higher risk of experiencing an asthma exacerbation despite being prescribed large doses of ICS, since the prescribed medicines were not effective at controlling their asthma. These patients are often described as having 'brittle' asthma. [72] Some patients may be incorrectly diagnosed with 'brittle asthma' when they may actually be non-adherent to their prescribed medicines.

Therefore, there are many other patient and treatment characteristics that may affect the relationship between asthma control, severity and the patient's risk of experiencing an exacerbation. These may include patient adherence, the age of the patient, changing severity, changes in the best practice for asthma care or the number of years that a patient has been treated for asthma. However, there is very little evidence to prove the effect of the duration of treatment on outcome.

2.2.7 Therapy related factors

Asthma medicines are known to be effective at improving asthma control in most patients, where the most effective medicines, prescribed and at the appropriate doses are defined within the evidence based guidelines available in the UK. [3] However, there are variations in the prescribing quality and the choice of drugs to prescribe that may also influence a patient's control.

Poor adherence to the evidence-based guidelines by the prescriber would be expected to result in poorer patient outcome. However, in some circumstances clinicians may make appropriate choices for, or with patients, based on the beliefs

and choices of patients, against the normative agenda of the guidelines. For this reason, inappropriate prescribing for individual patients is very difficult to identify and measure and to compare to outcome in a retrospective study design.

The selection of ICS prescribed to a patient may affect outcome, since different asthma drug substances may be more effective than others to some patients. However, one review of RCTs to compare the effectiveness of five different ICS was conducted by NICE, and the review concluded that there was no difference in clinical effectiveness between the different ICSs at low or high doses. [28]

2.2.8 Adherence to inhaled corticosteroids

Suboptimal adherence has been reported to be the single most important modifiable factor compromising treatment outcome in many conditions [9] and it is generally believed that the impact of improving adherence may be greater than improvements in specific medical treatments on the health of the population. [1] Medicine adherence is especially important in the treatment of asthma where the medicines available are proven to be effective and clear evidence based guidance is available for their appropriate prescribing.

A report by Horne et al. in 2005 summarised that "non-adherence to appropriately prescribed medicines is a global health problem of major relevance to the NHS."[1]

Improving adherence in asthma is especially important because as well as directly impacting a patients' asthma control and exacerbation risk, an increase in adherence can also lead to other benefits such as more tailored patient care and effective management of their condition, fewer unfilled or unused prescriptions, [1] which may

improve patient care and potentially clinical outcome. This will consequentially reduce unnecessary cost to the NHS, in medicines wastage and the treatment. This could include the costs of treating exacerbations resulting from non-adherence, extra tests or a step- up in treatment, and excess urgent care and hospitalizations. [73]

One study based in a regional difficult asthma service in Northern Ireland, using prescription refill records to measure whether patients filled at least 50% of their prescriptions, found that if hospital admissions could be avoided by targeting nonadherence in a population of patients with difficult to control asthma, a potential saving of £475 (£843–£368) per patient, per annum could be made. [74] This study also predicted that by improving adherence in these patients with difficult asthma, representing approximately 90,000 patients in the UK, a cost saving to the NHS of about £43 million could be achieved. An economic evaluation by Trueman et. al, in 2010, looking at all asthma patients found that over £130 million in treatment cost savings could be made by increasing compliance to 80% or above in the estimated 1.8 million non or partially compliant asthma patients in England. [75]

A review by Asthma UK in 2001, found about 18% to 48% of asthma deaths were caused by non-adherence [21] and it is often reported that poor adherence to ICS in asthma is the main cause or at least a significant risk factor for poor asthma control. [7 9] A small retrospective study of ICS adherence in 405 asthma patients was conducted in the US using medical records and pharmacy claims reported that 60% of asthma related hospitalisations were caused by 'less than perfect' adherence to ICS. [76] Underuse of medicines in asthma is generally associated with poor asthma

control, [1 9 10] and can decrease patient quality of life, and increase medical utilisation e.g. the cost of hospitalisation. [9]

Therefore adherence, especially to ICS in asthma patients, is an important factor in improving clinical outcome. Adherence itself may also be influence by other patient characteristics, which will therefore indirectly affect a patient's asthma control. These may include patient, socioeconomic and therapy related factors, but will also include the severity of a patient's asthma and previous exacerbations. One study of asthma patients conducted within one practice in a UK found that patients with mild to moderate asthma had an acceptable asthma outcome even if they were found to be non-adherent, but non adherence did affect outcome in patients with more severe asthma. [77] Adherence to ICS has been found to be lower in patients before an exacerbation of asthma than in patients with good control of symptoms, who did not experience an exacerbation. [78]

2.3 Medicine adherence and asthma control

There is a large quantity of literature that considers adherence to medicines, but adherence is often reported from various perspectives and studies are inconsistent in the terminology used and adherence is commonly not defined. [79]

Adherence is often viewed from one of two perspectives; whether the prescriber adheres to the current evidence based prescribing guidelines or 'best practice', or secondly, whether the patient adheres to an appropriately prescribed regimen for taking their medicine. This second perspective was the focus of this PhD study.

The term adherence has been used interchangeably in the literature with the terms compliance and concordance, when referring to 'adherence' to medicines, however, these terms emphasise slightly different considerations about the 'appropriateness' of prescribing for a patient and the relationship between prescribers and the patients (Table 2-1).

Table 2-1. Definitions for concordance, adherence and compliance

Term	Definition	
Concordance	Based on joint prescribing decisions ''where the doctor and patient agree therapeutic decisions that incorporate and respect their views."	Horne *et al.* (2005) [1]
Adherence	"The extent to which a person's behaviour- taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".	The World Health Organization (WHO) [80]
Compliance	"The extent to which the patient's behaviour matches the prescriber's recommendations".	Horne *et al*. (2005) [1]

The relationship between the patient and the health care provider is an important factor to effect a patients decisions about whether to take their medicines, where shared decision making [81] and feedback on adherence to the patient is believed to have a positive effect on adherence rates. [82] This ideal scenario where the patient and prescriber work together fits the 'concordance' definition of adherence.

The definitions of adherence and compliance rely on the assumption that the prescription or treatment advice has been given in the most appropriate way to benefit the patient, within the constraints of the healthcare system. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) consider the term 'medication compliance' to be synonymous with adherence, [83] defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen". [84] The term adherence will be used in this

PhD study using the WHO definition, which is consistent with the ISPOR definition and also the term recommended by Horne *et al*. in 2005. [1] Using this definition, the assumption must be made that the prescribed medicine was appropriate for the patient, but the benefit for this study is the potential to translate this definition into a quantitative measure.

2.3.1 Prevalence of low adherence in asthma

Adherence to ICS has been consistently reported to be suboptimal, with a large range of adherence rates, ranging from 30 to 70%. [85] The proportion of patients considered to have satisfactory adherence (often considered to be over 80% of days covered) has been reported to be as low as 18% [10] or 34%. [86] These reported low adherence rates show that improvements can be made to adherence in asthma which would be expected to improve asthma outcomes. The wide range of results recorded highlights the inconsistencies in the methods used between studies and the difficulties in measuring and comparing absolute adherence rates.

2.3.2 Interventions to improve adherence

Despite the high prevalence of non-adherence and importance of adherence in asthma to enable patients to have the best outcome possible, the interventions and methods used to treat or prevent non adherence are not well understood and consequently are not as effective as they could be. A literature review about adherence interventions across different conditions reported by Haynes et al. in 2008[11], and updated in 2014 by Nieuwlaat et al.[87] both came to similar conclusions that the current methods of improving adherence were complex and not very effective despite the efforts and resources that they consumed. Nieuwlaat et al also

found that that only 17 out of the 182 studies included in the review had a low risk of bias and only 5 of these reported improvements in both adherence and clinical outcomes. In these 5 studies, the interventions were complex and would be difficult to implement, leading the authors conclude that the interventions used were complex and not very effective. In 2005 Horne et al also reviewed studies that assessed the effect of interventions on adherence in addition to those studies reviewed by Haynes et al. and concluded that adherence could be modestly improved following an intervention, but there was 'considerable room for improvement'. [1]

A systematic review, published in 2017,[88] to review studies that tested interventions to improve adherence specifically in asthma, found that asthma education trackers or reminders to take doses and simplifying the dosage regime for taking their inhaler, led to an increase in adherence, however, this increase did not appear to translate into an increase in patient outcome (decreased asthma exacerbations, quality of life, absence from work/ school and asthma control).

The methods previously used to improve asthma adherence have included training to increasing patients asthma knowledge, [89 90] encouraging patients to monitor symptoms or peak flow and self management approaches, [90] identifying barriers to adherence, [90] self monitoring, [90] goal setting, [90] problem solving [90] and by improving the co-operative relationship between patients and doctors, where the doctor understands the patient's needs and constraints and they work together to devise a treatment regime (concordance). [89]

There are many reasons why individual interventions may have been unsuccessful, but most of the studies of interventions only focus on one factor effecting adherence, despite evidence that interventions to target more than one factor were found to be more effective in long-term conditions. [80] More complex interventions may be more effective at improving adherence [11] but need to be continued during treatment, which further increase the cost of delivering the intervention.

Most of the studies reviewed, also did not consider who these interventions should be targeted at, i.e. how to identify the patients who are at risk of poor adherence, or when the optimal time in treatment they should be delivered.

To understand how to improve adherence and to identify which patients we should target these interventions, it is necessary to understand the factors that may influence a patients' adherence. In chronic diseases such as asthma, this is further complicated because the factors influencing adherence may change over the long duration of treatment. The first step to study the differences that effect a patients adherence is to quantify adherence using a suitable measure.

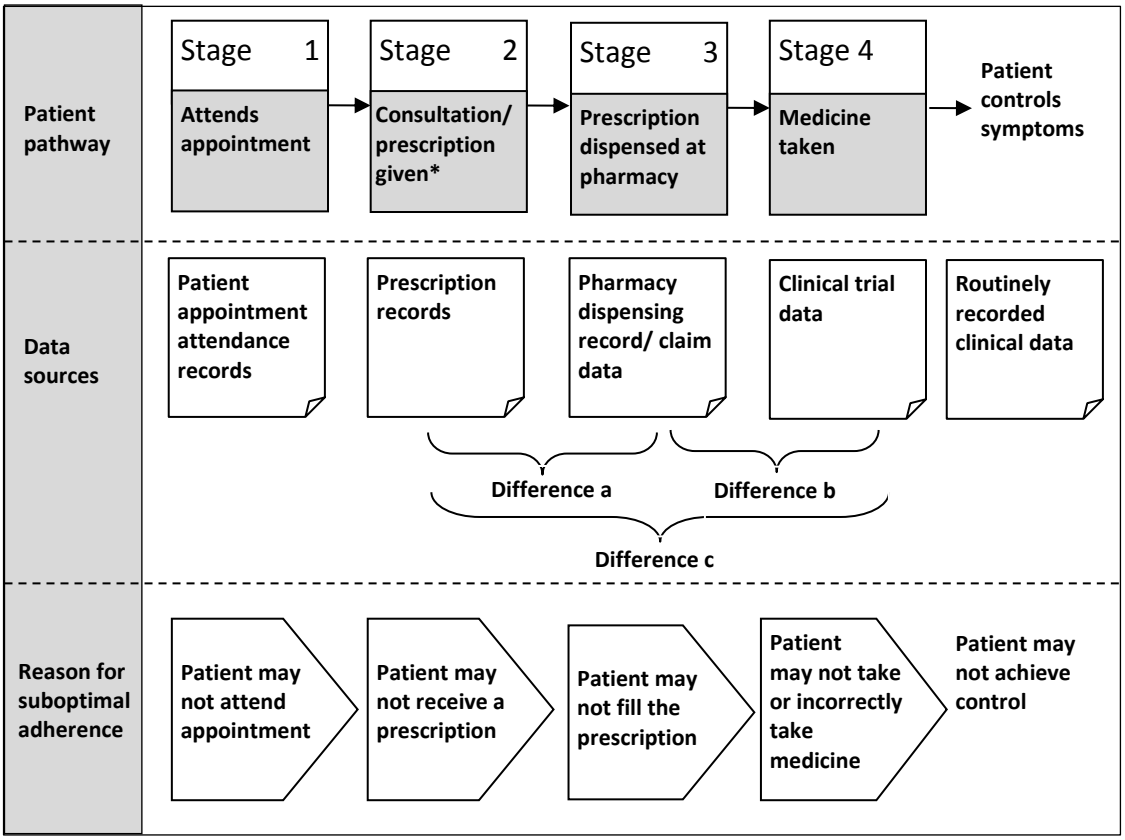
2.3.3 Measurement of adherence

The consequence of a person's behaviour affecting their choice about whether to take their prescribed medicine can be measure using the percentage of doses of medicine taken as prescribed to represent adherence. [84] To calculate this percentage, information about how much medicine a patient had taken and how much medicine they were, or should have been prescribed must be collected. Information about an individual patient's medicine utilisation can be collected

prospectively alongside a randomised control trial (RCT) or retrospectively, such as using routinely recorded clinical data.

Alternatively, within 'normal' clinical care, data to represent the amount of medicine taken by the patient can be collected at each of four main steps in the patient pathway of accessing medicines (see Figure 2-1).

Figure 2-1. The stages of accessing medicines



***or repeat prescription requested and received.**

The measurement of adherence and information gathered at each step can provide information about the mechanism for non-adherence, such as whether the patient attended the appointment, whether the patient requested or received more medicines from the prescriber or at the pharmacy, or how the patient took their medicine, for example under dosing daily or missing doses.

Measurement at stage 4 is often considered to be the most accurate measurement point for adherence since it is the most direct measure of the amount of medicine that the patient actually takes. At each step the patient has a further opportunity to be non-adherent to their recommended treatment. Therefore, measurement at any earlier stage is likely to overestimate the amount of medicine taken, because any further opportunity for the patient not to take their medicine as prescribed or recommended is not considered.

The difference in the amount of medicine measured by prescriptions dispensed (stage 3) and actual medicine taken (stage 4) represents a patient who filled the prescription but did not take the medicine.

The difference between the total amount of medicine measured by prescriptions issued (stage 2) and prescriptions dispensed (stage 3) represents a patient who received a prescription, but did not fill the prescription. This is known as primary non-adherence, which can have a significant effect on measured adherence. A retrospective study in Canada between 1997 and 2004 using both prescribing and prescription fill data from an administrative database, found that 35% of days' of supply prescribed for ICS in the treatment of asthma had not been filled. [91]

There are two main options for collecting data about adherence. The first is using prospective data collected within randomised control trial (RCT). The second is to use retrospective data, to represent medicine use, by using data recorded at earlier steps in this process of accessing medicines.

RCTs were considered to be the 'gold standard' method for testing adherence, by measuring the actual amount of medicine taken by the patient, however, only relatively small populations can be studied, over relatively short time periods in a setting that is not 'usual' clinical practice.

2.3.3.1 Prospectively measuring adherence

Prospective data collection methods including patient self-reporting, biochemical methods, physician opinion, medication measuring, or electronic monitoring devices [92] have historically been used within an RCT to directly or indirectly measure patients' actual medicine taking (Table 2-2). These prospective methods are considered to be the closest estimation of actual medicine taking. To calculate adherence, the amount of medicine taken is viewed alongside the amount of medicine intended for the patient to take, which is generally recorded by the prescriber.

Table 2-2. Prospective adherence measures

Adherence Measure	Advantages	Disadvantages
Biochemical methods **Drug Assays.**	Direct measurement- the only measure that confirms actual medicine use.	High cost and invasive for patients. Not available for all drugs, only asthma drug is theophylline. [85] Effected by patient, age, pharmacokinetic factors, drug absorption, tissue distribution and renal elimination. [93]
Self-report **Patient reporting maybe in diaries, interview or questionnaires.**	Simple, inexpensive and brief. [85] Questionnaires can differentiate between intentional and unintentional adherence.	Variable degree of accuracy. [85] Overestimates adherence 50% of the time. [94 95]
Physician opinion **By judgment of patient's adherence.**	Forms part of usual clinical care.	Thought to overestimate adherence. [80]
Medication Measurement **Counting pills, weighing canisters or liquid**	Simple to collect in a clinical trial setting.	Results can be distorted by medicine dumping or sharing of medicines within a household. [85 93].
Electronic measuring device **Devices which record the date and sometimes time of each medication use.**	Thought to offer the most accurate measure. [93]	High cost Can only be used in a clinical trial setting and on some dosage forms. Patient consent to monitoring may affect patents behaviour.

Prospective data collection aims to accurately record the amount of medicine that should have been taken, and also enables information about reasons for non-adherence to be gathered. However, there are several limitations associated with the practicalities of these methods. In RCTs, the measure of patients' adherence could be biased by the 'Hawthorne effect' [96] when patients are aware that their adherence is being monitored or measured, and may consequently increase their adherence. Additionally, clinicians, or practices that choose to take part in RCTs may not be a representative sample of clinical practice in the UK making the results biased. RCTs can also be costly and time consuming, especially for studies with a long time frame, [97] and many measures are not practical to be used for a large population. [97]

2.3.3.2 Retrospectively measuring adherence

In contrast to RCTs, the use of retrospective measures of adherence using data collected during routine clinical care, such as dispensing or prescribing records, are considered to be relatively inexpensive and accessible [98] (Figure 2-1). Although, adherence measured in this way can only be considered to be a proxy measure to represent patient's adherence since actual medicine taking is not measured. But by carefully constructing the adherence measure using careful definitions of the calculation, the measure can be a good representation of adherence (Table 2-3). Administrative data from a claims based system or electronic medical records, are routinely collected for a large population of patients and over a long period of time, so it enables the study of changes in adherence over time and the investigation of the factors that may affect adherence. Adherence measured by routinely collected

data within a clinical setting can also avoid selection bias and the Hawthorne effect, as patients are not aware that their adherence is being monitored or measured.

A variety of measures have been used in literature to measure adherence or medicine use when using retrospective databases. Each measure attempts to characterise a different aspect in the mechanism of accessing medicines, to determine to mechanism for how less than 100% of the intended medicine was taken. This was reported by number of systematic reviews by Steiner and Prochazka (1997) [97], Andrade *et al.* (2006) [99] and Peterson *et al.* (2007) [83]. These measures can be summarised into six main categories (Table 2-3). The most commonly used methods are the MPR and the PDC.

Table 2-3. Retrospective adherence measures used in observational studies

Measure	Data used	What does it measure?	Notes
Medicine Possession Ratio (MPR) [100] or cumulative medicine availability (CMA)	dispensing data	The proportion of medicine that was dispensed compared with the quantity intended to be used in the same time period.	A commonly used measure of medicine adherence. [89, 92]
Prescription Possession Ratio (PPR) [101]	prescribing data	The proportion of medicine that was prescribed compared with the medicine that should have been prescribed to that patient.	Useful when prescription refill data is not available.
Proportion of Days Covered (PDC)	Prescribing or dispensing data	A similar method to MPR, but excludes the double calculation of days when prescriptions overlap, [83] therefore, PDC cannot exceed 100%.	Most useful for treatments when the remaining medicine is expected to be discarded once a new prescription is issued, often when medicines are frequently changed. PDC and MPR are often used interchangeably.
Proportion of Prescribed Days Covered (PPDC)	Prescribing and dispensing data	Measures the proportion of the doses prescribed that are filled.	This measure represents primary non adherence. [91]
Persistence	Prescribing or dispensing data	The duration of time that a patient has taken a medicine above a chosen tolerance level of adherence for without stopping.	Useful for treatments where there is a known duration that the medicine needs to be taken for it to be considered to be effective for example anti-depressants. [97 98] Also useful for duration of use studies.
Cumulative medication gaps (CMG)	Prescribing or dispensing data	A measurement of gaps in medicine availability to the patient. (Non-adherence).	Most appropriate for medicines that require constant use. Some medicines may have little clinical consequence of a short gap such as 3 days [98] but for other medicines this may be important.

Some studies use a cut off level to translate the continuous measure of adherence into a categorical one, where patients are categorised as adherent or not adherent. A cut off level of 100% adherence is not usually selected since patients may have a 'good' outcome at lower adherence levels. We know that for patients who are appropriately prescribed an ICS to control their asthma, at low ICS adherence levels, a patient's asthma will not be adequately controlled, but as adherence approaches 100%, the patient will receive an adequate therapeutic dosage to gain control of their symptoms. Across all conditions and medicines a cut off level of 80% is often chosen when an MPR is used. [10 102]

However, many factors can affect adherence levels and the significance of this adherence level on clinical outcome in patients including; the data source and method of measurement used, the medicines and the outcomes for the condition being measured and other patient characteristics. Using different data to measure a proxy for adherence may alter the absolute values of adherence measured, i.e. adherence may be higher when measured using the quantity of medicine prescribed than using the quantity dispensed. The impact of non-adherence on the therapeutic concentration will differ between medicines with different pharmacodynamic and pharmacokinetic profiles and this will have different effect on patient outcomes in different conditions. The effect of adherence level on the patient's outcome may also be effected by patient's with different characteristics including age or gender. Therefore, it is more appropriate to use adherence as a continuous variable unless a level of adherence where there is a clear difference in the effect on outcome can be identified using the same data and the same method of measurement. A report for

the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) recommended that a cut off level should not be used unless empirical evidence exists to validate the level. [83]

2.3.4 Measuring asthma adherence to inhaled corticosteroids using retrospective data

In a review of the studies to measure adherence to ICS in asthma patients using secondary data sets, 21 studies were found to measured adherence using a variety of methods. The studies were found to measure a number of different aspects of adherence, including the effect of adherence on clinical outcomes, or the use of rescue medicines, or the effect of other variables on adherence, such as the type of ICS or other medicines prescribed (Appendix 4).

In the studies were outcome was considered, poorer adherence was associated with poorer patient outcome, including hospitalisation, [76 103-106] but one study found that adequate adherence was not associated with the use of less rescue medicine. [107]

Dispensing records were used to measure adherence to ICS in asthma patients, especially in studies conducted in the US, Canada, Sweden and the Netherlands, where pharmacy dispensing data is often available with linkage to a clinical data in claim data bases. [12 91 106 108] These studies usually report adherence using an MPR, with a wide spread of results from 22% to 73%. [76 109-112] However, most studies reported the proportion of patients that met the criteria for being adherent (often 80% was used as the cut off), ranged from 11% to 46%. [10 86 113-115] Adherence was also sometimes reported as proportion of days covered (PDC) (ranging from 24% to 37%[104 116]) or simply the number of prescriptions filled. [103 117]

The linkage of clinical data and prescription fill used in some studies also allows the evaluation of the effect of other prescribed medicines on adherence [108], prescribing patterns [12], and the effect of adherence on outcome. [12 91 105 106 108]

The health care systems in countries such as the US, Canada, Sweden and the Netherlands are generally quite different when compared with the UK. The data linkage available in these countries also allows the investigation of primary non adherence, i.e. whether patients fill their prescriptions, measured by the proportion of prescribed days covered (PPDC), which divides the number of days' worth of prescribed medicine dispensed by the number of days' worth of medicine prescribed and ranged from 26% to 64%.

In the UK there were very few retrospective adherence studies conducted where adherence to ICS was measured. Dispensing data with linkage to clinical data is not widely available in the UK but is commonly used in other countries to calculate an MPR.

Two observational studies used prescribing data to measure adherence to ICS in patients with asthma over a short period of time in the UK. [107 118] A study by Elkout [107] used a 'practice team database' (3172 patients) to investigate the effect of adherence on rescue medicine use. Elkout found that only 15-39% of patients had a PPR between the range of 80% to 100%. Another study by Murphy [118] used a small data set from a difficult asthma service (161 patients) to evaluate the relationship between patient variables including clinical outcomes and adherence. Murphy reported a mean PPR over a duration of 12 months of 65.2%.

Some of the studies reviewed did measure both adherence to ICS (some also included other preventor medicines) and a clinical outcome measure [12 76 91 103 104 107 112 118] and most of the studies report adherence measured over a single interval, [10 104 110 111 113-116 119] or over two or three annual intervals. [109 112] One study by Williams *et al*. (2011) [106], used a series of measures over time to investigate the effect of adherence on clinical outcome, but this study only measured primary non-adherence and only included a small cohort of asthma patients (n=298). Therefore, the long-term pattern of adherence to medicines in a long-term condition such as asthma, remains unclear, especially to understand the complex relationship between adherence and clinical outcome.

In summary, of the studies found to investigate patient adherence to ICS using retrospective prescribing or dispensing /claim data, adherence was not measured in multiple intervals, and few studies compared adherence between patients with different characteristics or clinical outcomes. Where calculated, the variables were often measured over these same intervals which makes it difficult to understand the causual relationship between adherence and clinical outcome or other time dependent patient variables.

2.4 Causes of poor adherence to inhaled corticosteroids

Despite the limited number of studies considering the effect of other variables on adherence to ICS over time, many previous quantitative and qualitative studies and literature reviews identified reasons for non-adherence to asthma medicines. [85 120 121] However, the findings were often inconsistent, and many factors partially

associated with poor adherence have not been extensively studied specifically in asthma patients or for ICS adherence.

Alongside the factors associated with differing adherence levels in patients, poor adherence can be considered to be intentional or unintentional. Unintentional adherence is caused by external constraints that effect a patient's ability to follow the regime include the patients capacity, resources and opportunity, [122] for example problems with access (e.g. Cost, distance) [1] and forgetfulness [90]. However, poor motivation to take a medicine may also increase the likelihood of forgetting. [1 123]

Intentional non-adherence is caused by the patient's attitudes towards taking their asthma medicines, based on their beliefs, perceptions, knowledge of their condition and their expectations, as described in the Health Belief Model. [124-126] However, it is the clinician's responsibility to ensure that these decisions are being made in an informed way (informed choice), to ensure that the patients' best interests lie at the centre of any choices made. The British Asthma guidelines [3] consider that patients may "wish to balance the aims of asthma management against the potential side effects or inconvenience of taking medication necessary to achieve perfect control." This suggests that poor adherence is not always negative, for example, where an informed patient has chosen not to take their medicine.

A patient's beliefs are an important determining factor of patient adherence to their prescribed medicines. [1] The effect of patient beliefs on adherence are difficult to measure, but both the intentional and unintentional causes of low adherence to ICS are expected to be associated with other patients characteristics which can be measured. Some of these characteristics may directly affect adherence, (e.g. by the

patient ability to pay for their prescription), or may indirectly effect adherence, by affecting the patients choice or motivation to take their medicines.

The WHO list five categories of factors that influence adherence; patient related, condition related, therapy related, health system related, and socioeconomic status related factors. [9] Evidence for the effect of patient characteristics on adherence is presented in the following five sections.

2.4.1 Patient related factors

2.4.1.1 Demographic

Patient demographic factors including patient gender and age and ethnicity are expected to influence adherence to asthma medicines.

It is generally believed that female asthma patients have higher adherence than males, however, across studies of adherence the findings have been inconsistent. [127]

The age of a patient was reported to have a complex association with adherence, for example, adolescent asthma patients (age 12-17 years) were reported to have a lower adherence that other age patients. [128 129] The elderly also be expected to have lower adherence, due to difficulties in memory and their ability to take their medicine, and are likely to have other medicines prescribed for comorbidities which may also affect adherence. However, even across different conditions, there is no evidence is to suggest that adherence is different between the elderly and young adults. [130]

Adherence in children, especially in younger children is expected to be the responsibility of parents; therefore the characteristics of parents may also affect the

child's adherence. Children with asthma take increasing responsibility for their adherence as they grow older. [63 128]

Ethnicity was reported to be associated with adherence to ICS in patients with asthma; for example, one study reported a lower adherence in patients with an African American ethnicity than patients classified as non- African Americans [131] or non-native speaking adults. [132] However, other measurable or unmeasurable patient factors may also attribute to this difference such as socioeconomic status, language problems or the patients beliefs about medicines.

2.4.1.2 Lifestyle and comorbidities

Patients lifestyle factors including whether they smoke, or are exposed to cigarette smoke and their BMI, and whether they have other conditions that are being treated, including pregnancy are also expected to influence whether patients adhere to their prescribed asthma medicines.

No direct evidence to associate smoking with adherence was found. Smoking could be considered to be a risk taking behaviour similar to non-adherence, which would suggest that smokers might be less likely to adhere than non-smokers. However, smoking is believed to effect asthma control because of the reduced efficacy of ICS, [53 54] this may increase adherence in smokers, especially if the patient becomes more symptomatic.

Adherence to all long-term therapies are likely to be affected if medicines are required to treat comorbidities, but very little research was found to report the effect of multiple conditions on adherence in chronic conditions such as asthma. [133]

Specific comorbidities may affect adherence in asthma such as depression. Bender *et al.* (2006) [134] reported there was evidence that depression and risk taking behaviour were associated with non-adherence in asthma.

Pregnancy has been found to be associated with a reduction in adherence to ICS. [135] In a study of 1282 patients using questionnaires and patient pharmacy records, patients with a BMI that is not considered to be in the 'normal' range (a BMI of 18.5 to 25) were found to have a reduced adherence, especially patients with a high BMI (of over 25). [50]

2.4.2 Socioeconomic status related factors

Socioeconomic status is believed to influence how well a patient adheres to their asthma medicines. Prescription co-payment exemption is also expected to influence adherence, some patients with high deprivation are exempt, but also are patients aged 60 or over or under 16 (up to 18 years if in full time education), or who are pregnant, or have a comorbidity with an exemption. [136] This is especially important for asthma patients in the UK who do not fall into these categories, since they are not entitled to a 'medical exemption' from their prescription charge with an asthma diagnosis, available for patients with other chronic diseases such as diabetes or epilepsy.

Socioeconomic status has been found to significantly affect adherence to asthma medicines, [80] where a higher socioeconomic status derived from using multiple measures including household income and education level, was a strong predictor to lower adherence to ICS. [63] However, household income alone was not found to affect adherence significantly. [63] The measurement of the effect of SES on

adherence may be effected by the method of SES chosen for an individual study as discussed in Section 2.2.5.

A patient's access to free prescriptions is expected to affect adherence. In the US, a retrospective cohort study across multiple conditions found that the introduction of a small prescription co-payment reduced the number of filled prescriptions. [137]

2.4.3 Condition related factors

Adherence to ICS may vary between patients with different levels of severity and symptoms control including the occurrence of an exacerbation. However, the evidence to support the effect of severity on adherence is inconsistent.

The occurrence of an asthma exacerbation would be expected to result in increased adherence; however a systematic review of inhaler adherence in asthma reported an inconsistent effect on adherence between studies. [14] Another review of asthma adherence studies found that patients who were previously hospitalised for their asthma were reported to have higher adherence than those who were not hospitalised, maybe due to a change in the perceptions of the patient about the seriousness of their condition. However, this increased adherence does not appear to be sustained for long following hospitalisation. [85]

The nature of asthma means that many patients with well controlled asthma will have few daily symptoms, but may still experience acute symptomatic periods, may lead to patients perceiving their condition to be intermittent. [138] Due to this intermittent nature of asthma, patients may believe themselves to be well when they have no symptoms and are less likely to adhere to preventer medicines, such as

ICS routinely, which is likely to increase the frequency of exacerbations, which may increase reliever medicine use such as SABA in response to symptoms. [1]

Patients with severe asthma are expected to be more likely to adhere to ICS than patients with mild asthma [14], because patients with more severe asthma are likely to be more symptomatic i.e. are more likely to experience an exacerbation of symptoms, and in response, they would have a greater incentive to adhere to prescribed treatment. However, some patients with asthma may appear to be uncontrolled by their treatment regime prescribed, but could be actually non-adherent to those medicines, so may be treated at a higher step that would be necessary. In contrast, patients with mild asthma may only have minor clinical consequences of non adherence to medicines, [120] therefore they may choose to live with occasional asthma symptoms rather than adhere to their daily preventer medication. [139]

In any chronic condition, the long duration of treatment adds a further dimension to the interactions between patient characteristics and adherence because factors affecting adherence could change over the course of treatment or over time, for example, asthma severity, patient's beliefs, control of asthma, the occurrence of an exacerbation or previous levels of adherence. Over time, patients also get older and may have increasing numbers of comorbidities.

Some studies have reported that adherence to ICS decreased over time, but these studies were generally conducted over a limited period of time, [63 140 141] which are not able to inform us about the trend over treatment for a chronic condition such as asthma.

2.4.4 Therapy related factors

Patient adherence may be influenced by the treatment that they receive to treat their asthma. The drug class and the drug substance prescribed, the method, quality and complexity of administration and patient concerns about adverse effects may affect adherence.

Inhaler technique is important since asthma patients may not receive the correct dose of ICS due to poor inhaler technique, even though they intended to take the medicine. [3] Different inhalers require different techniques, for example a metered dose inhaler requires coordination between breathing and actuation when compared with a breath actuated inhaler, this is important especially for the elderly or patients with poor manual dexterity. [142] If a patient does not receive the correct dose, they may have a poor outcome despite having seemingly 'good' adherence. Therefore training on inhaler technique is important. [3]

The local or systemic side effects of ICS, are usually rare such as a reduction in bone density, growth restriction in children, glaucoma, cataracts and oral candidiasis. [3] These side effects are usually associated with using high doses (400 micrograms BDP a day or equivalent) over a prolonged period. [44] Despite the relatively low risk of these side effects, it has been reported that patients still have concerns about steroid use and this 'steroid phobia' may cause patients to reduce or stop taking their ICS. [120] In general, non-adherence could be a response to concerns about side effects of the ICS, when patients balance up the perceived necessity and concerns to minimise their use of prescribed medicines. [1]

Asthma treatment often includes a combination of 'preventer' type medicines (e.g. ICS) to control the condition and 'reliever' type medicines (e.g. a SABA), to treat symptoms. The regimen for when and how to take medicines can be complex and patients may not understand or may forget the instructions about when and how to take the medicine or the importance of adherence to the medicine. [80] In asthma, adherence to medicines was been found to be lowered with more frequent dosing and with increased complexity of the regimen. [85]

Patient's preferences such as perception or taste of a particular ICS could also affect whether the patient chooses to adhere to that particular ICS. Very little research has been carried out to understand these differences, where ICSs are considered as a class of medicines, or single ICS drug substances.

Time to the onset of effect of medication can also influence patients' adherence to medicines, where patients may choose to use a SABA instead of their ICS because they can feel an immediate effect of the medicine. For example, ICS have a delayed clinical impact, usually 3 to 7 days after initiation, [44] consequently, adherence to ICS is likely to be relatively lower than adherence to bronchodilators that relieve symptoms within a shorter time period. [93] The treatment of symptoms is not considered to be either the most clinically or cost effective method of care, where patients who rely on a SABA or a LABA, instead of using their prescribed ICS daily, have been found to delay in seeking medical advice and is therefore not recommended. [143]

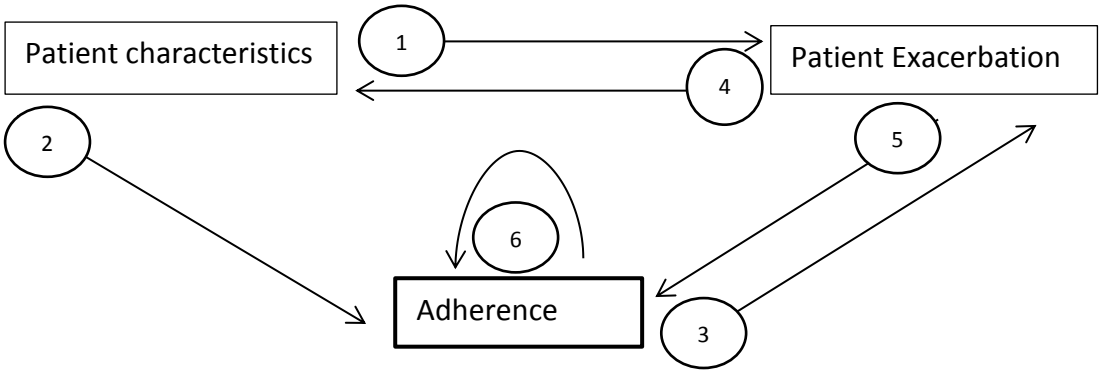
Patients may also choose to use alternative methods to control or treat their asthma, such as avoiding triggers, or using emergency treatment at either primary or

secondary care to treat exacerbations rather than trying to prevent them from occurring.

2.5 Summary

In summary, adherence to ICS is important in the successful treatment of asthma. There is clearly a complex relationship between a patient's ICS adherence, and other factors that may also affect the patient's adherence including whether the patient has experienced an exacerbation, and their asthma severity (Figure 2-2). Since asthma is a chronic disease, these relationships may change over time.

Figure 2-2. Relationship between an asthma patients characteristics, adherence and clinical outcome



1 Patient characteristics can affect exacerbation occurence, which may also be affected by adherence and over time being treated.

2 Patient characteristics can affect adherence, which may also be affected by patient exacerbation occurence and over time being treated.

3 Adherence can effect patient exacerbation occurencee. This could be affected by other patient characteristics and over time being treated.

4 The patients outcome can effect the patients characteristics such as their perceived severity or prescribed medicines

5 Whether a patient experiences exacerbation would be expected to affect future adherence.

6 A patient's previous adherence would be expected to affect future adherence, since many of the characteristics that would affect adherence, including those that cannot be measured, would be remain constant over time.

Many of the causes of poor adherence are not well understood, especially how the relationship between adherence and other factors may change over time. The

variables believed to affect adherence include: gender, age, socioeconomic status, region of living, marital status, prescription exemption, smoking status, comorbidities, pregnancy status, BMI, patient beliefs, characteristics of the condition, severity of asthma, change in severity, control of asthma, exacerbation occurrence, adverse effects from ICS/OCS, drug substance, complexity of treatment.

Using retrospective data, allows a large cohort to be included in the study to investigate the subgroups of each characteristic as well as enabling the patients treatment within a real clinical setting to be followed for a much longer period of time than an RCT would allow. It is important to have enough patients within each individual subgroup to increase our confidence in that any difference between adherence in these subgroups is statistically significant and not biased by individual extreme results, that would have a greater influence on the results in a smaller population.

Before analysis, an appropriate data set, the cohort and methods to create each variable were selected and developed in Chapters 3 to 5. This includes the development of a variable to measure adherence to ICS in asthma patients which can be measured over time and a validation of the methods selected, since this type of measure had not been previously generated. Then to investigate the effects of different variables on adherence and how these relationships may change over time suitable methods were explored, including the 2 way relationship between adherence and patient variables, and the use of a multivariate regression model using panel data to allow for the effect of time to be included, which has not previously been applied in this type of study.

Chapter 3 Cohort selection and data management

3.1 Introduction

To research the relationships between adherence and patient characteristics and outcomes of asthma control using an observational study, the data source, study cohort and study variables must be defined and then, the quality of data and characteristics of the available variables should be explored to ensure the suitability of this data set for research purposes. [144]

A variety of variables related to patient characteristics, socioeconomic factors, characteristics of the patients asthma condition and the therapy prescribed that could affect either adherence or clinical outcome or both variables (Table 3-1), were identified from literature review (Chapter 2). However, the characteristics of these variables and how they may change over time are unknown.

Table 3-1. Variables associated with adherence to ICS or clinical outcomes of asthma control

	Parameter and Definition	Adherence
Patient related- Demographic	Gender	?
	Age	✓
	Ethnicity	✓
	Marital Status	?
	Region of living	?
Patient related- Lifestyle	Smoking Status	?
	Pregnancy status	✓
	BMI	?
	Comorbidities	✓
Socioeconomic related	Socioeconomic status	✓
	Prescription charge exemption	✓
Condition related	Severity of Asthma.	✓
	Control of asthma	?
	Duration of treatment	✓
	Clinical outcome	✓
Therapy factors	Adherence to treatment	n/a
	Type of ICS drug substance	?
	Adverse effects from ICS/OCS	✓
	Complexity of treatment	✓

3.2 Aim and objectives

This chapter assessed the availability of data for the variables that are believed to affect adherence to ICS and explore the time-dependent characteristics of these variables. The objectives included:

- To define and justify the data source (CPRD and HES data linkage) used in the study
- To define and select the study cohort from the dataset
- To define and identify the variables in the cohort data related to patient characteristics that are associated with adherence in asthma.
- To understand the quality and basic characteristics of the derived variables including their trend over time.

3.3 Data source

In this study CPRD and HES data linkage was chosen.

Ideally, to study the factors associated with medication adherence in patients using retrospective data, individual patent data from claims based data sets or electronic patient records that contain information about medicine use (or at least medicine collected by the patient), clinical outcome and other patient data would be used. However, since individual patient's claims data and prescription fill records are not available in the UK, prescribing data is considered to be a suitable alternative.

There are several datasets in the UK where routine primary care data are recorded such as the Clinical Practice Research Data link (CPRD), the QResearch database and The Health Improvement Network (THIN). [145] The Clinical Practice Research Data

link (CPRD) can provide linked clinical records within secondary care data from the Hospital Episodes Statistics (HES) database that provides information of patients requiring hospitalisation, this enables the more severe asthma exacerbations to be identified from the data.

3.3.1 Clinical Practice Research Data link

The CPRD is a large computerised database of anonymised longitudinal medical records from a general practice primary care setting in the UK. The CPRD contains data prospectively collected within primary care and is converted into a coded database by the CPRD team.

The original database was only populated by its developer, a general practitioner, Dr Alan Dean. In 1987, Value Added Medical Products (VAMP) developed the database to include more practices. In late 1993, VAMP was taken over by Reuters, who gave the database to the office for Population Censuses and Statistics (OPCS) in early 2004 (now the Office for National Statistics (ONS)), [146] the database became known as the General Practice Research Database (GPRD). The data is now hosted and managed by the Medicines and Healthcare Products Regulatory Agency (MHRA), as an e-health secure research service called the CPRD. [147]

The database is now extremely large, including over 11.3 million patients in 2015, approximately 6.9% of the estimated UK population with records collected from 674 primary care practices throughout the UK. [148] This database population is considered to be reasonably representative of the demographic characteristics of the UK population and is considered a valid source of data for epidemiological analysis for respiratory disease. [22] The database has been used, mainly to study

drug safety, but has been used increasingly for pharmacoepidemiology studies. [149] Several studies have used the CPRD to report the prevalence of asthma. [22 150]

The CPRD group has obtained ethical approval from a Multi-Centre Research Ethics Committee (MREC) for all purely observational research using CPRD data. However, any studies using the CPRD data which are destined for publication or for which it is intended to communicate the results to third parties, must receive Independent Scientific Advisory Committee (ISAC) approval on the scientific quality of the protocol before proceeding. The protocol for this PhD study was granted ISAC approval on the 25th March 2013 (number 13_036).

The CPRD data are arranged in a 'long' format, where patients can have multiple rows of data to record different details about each visit. Each row of data has a date for the event and a unique patient identification number to link a patient's data together. The information is recorded as part of routine GP practice based on Read codes, and product codes for prescriptions. Read codes are coded clinical terms, maintained by the UK Terminology Centre (UKTC). [151 152] The CPRD recode these Read codes as medical codes in the data. Product codes are unique identifiers of either generic or branded products and provide information on formulation and strength. [152]

The CPRD organises the data into several files to record different types of information about the medical services provided in the primary care setting (Table 3-2). The patient records are linked by individual an anonymised patient identification number.

Table 3-2. The CPRD files and data included in each file

File name	Data included in file
Patient	Patient unique coded identifier (patid), gender, date of birth, marital status, family ID number, Child health surveillance number, prescription charge exemption, deprivation by patient, date when patient first registered with the practice, transfer out dates and periods, death date and data acceptability indicator
Practice	Practice coded id, region, date of last collection for the practice and the date when the practice was considered to be up to research quality
Staff	Staff coded identification (staffid), gender and role
Consultation	Patid, event date (and the date it was added to the system), type of consultation, consultation identification number, staffid, duration of consultation
Clinical	Patid, event date (and the date it was added to the system), staff id, consultation identification number, medical code (Medcode#), free text, episode type and any additional information linked to this event
Referral	Patid, event date (and the date it was added to the system), staff id, consultation identification number, medical code (Medcode#), free text, source of referral, referral specialty, referral type (in patient, day case etc.), description of type of event (first visit, follow up etc.), urgency
Test	Patid, event date (and the date it was added to the system), staff id, consultation identification number, medical code (Medcode#), free text, test results and unit of measure
Therapy	Patid, event date (and the date it was added to the system), staff id, consultation identification number, product code (Prodcode), free text, BNF code, quantity, numerical daily dose, number of days of treatment, number of packs, pack type, issue sequence of a repeat prescription

#The Medcode is a code used by the CPRD that can be linked to the medical Read code (via a CPRD look up file) to represent the medical term that was chosen by the GP to be recorded.
$ The Prodcode is a code used by the CPRD that can be linked to the Multilex product code (via a CPRD look up file) to represent the medicine/ product was chosen by the GP to be recorded.

The CPRD provides an acceptability indicator for the data to indicate when the practices records were considered to be up to research quality. This assessment is undertaken centrally by CPRD using their own algorithm, essentially using a check list of data quality markers determined as practices periodically submit their patient data for processing. [153] Only up to standard records were used in this study.

3.3.2 Hospital Episode Statistics

HES data contains records for individual patients to record admissions, outpatient appointments and accident and emergency attendances at English NHS hospitals from 1 April 1989 and outpatient attendance data from 2003. [154]

The CPRD data is linked via the anonymous patient identification number to Hospital Episode Statistics (HES) data, for patients registered at practices in England (not the whole UK) who have consented to this linkage with HES data. The proportion of the UK CPRD that had consented to data linkages including HES in 2015, was 58%. [148]

The HES data records use the International Statistical Classification of Diseases and Related Health Problems, version 10 (ICD-10) clinical coding and Office of Population Censuses and Surveys, Classification of Interventions and Procedures version 4 (OPCS4) procedural coding. [152]

The data is presented in a 'long form' where each row of data records the treatment for an individual patient on a ward, described as a consultant "episode" of care. Single or multiple episodes may be included in a single hospitalisation (known as a "spell" in HES). The data is arranged in files relating to hospitalisation episodes, and other files for events that are linked to specific episodes such as the primary diagnosis for the hospitalisation, or individual episodes. [154] No details about medicines received at hospital are recorded. The HES data file for primary diagnosis was used for this study.

3.3.3 Pros and cons of using the CPRD linked with HES data

The CPRD is a rich source of clinical data including a large number of patients, over a large time period. This can enable studies about drug utilisation or efficacy to be conducted that may be not otherwise be possible. Additionally, the ability to look at the CPRD data linked to secondary care records within a 'normal' clinical setting allows a comprehensive follow up of a patient's clinical treatment.

Alongside the major advantages that the CPRD data can provide; there are also some important limitations.

The first limitation is that CPRD records are manually inputted so are subject to human error and interpretation when they were recorded. This could cause anomalies in the data for individual patients, but as long as the errors were random and not biased, the large quantity of data available should make these errors only have a negligible effect on the outcomes.

However, inconsistencies that could cause bias in the data entry could be also be caused by factors that give incentives to record specific data and lower priority to others. For example, GP performance indicators such as the Quality Outcomes Framework (QOF), introduced in 2004, [154] may increase or decrease the recording of certain patient or clinical information. This may mean that some variables such as smoking status or specific diagnosis codes for selected conditions are more complete or accurately recorded than others.

Additionally, the data is intended to be a medical record of the treatment and details for the patient, not specifically for research, therefore only data that is relevant to the current treatment at the time of recording is available. Therefore studies using this data need to be designed to use the data that is available and may have to make compromises and use proxy measures for variables instead of direct measures.

Patients can move to another practice; therefore the patients may enter the practice after the start of treatment or may leave the data. This will results in some

patients in the cohort having right or left censoring, which must be considered in the study design.

Only primary care prescribing data is included, prescribing in secondary care is not available, neither is an emergency supply of medicine acquired at a pharmacy. This could affect the results by showing a lower use of medicines during or following an exacerbation when the patient is admitted to hospital. There is also the possibility that medicines could be accessed from elsewhere. However, this is considered to be only a small number so should not significantly influence and results.

The proportion of the CPRD practices that have allowed data linkage of their records with the HES data, may not be representative sample of practices, especially since this liked data is restricted to practices within England. The HES data is only available from April 1997, therefore if the study includes CPRD data prior to this date, the linked HES data will be missing, this must be considered in the study design and any findings if earlier data is included.

Despite these limitations, the large volume of available data outweighs many of these limitations since it allows the impact of any anomalies in the data on the conclusions to be minimised, especially when the conclusions are drawn at a population level. However any limitations that may cause bias in the results must be considered when making conclusions and their effect minimised in the study design.

3.4 Methods

3.4.1 Study design

The cohort was defined and selected and the variables required for the study (Table 3-1), were derived and developed for each patient, for each year that they were included in the cohort.

This cohort study uses a panel data structure, repeated at annual cross sections. The advantage of this data structure is that it allows changes in the variables to be measured over time. However, a suitable time for the repeat measure had to be selected. Prescriptions may not be filled immediately after they are received by the patient and large quantities may be prescribed to cover an extended period of time. Therefore, an annual interval was chosen to reduce the effect of this time delay by combining the records over a year. Other variables used in the study may also show a large amount of variation over time if the interval length was shorter than one year, caused by factors (that may not be recorded in the patient records), which could affect patients in the cohort differently, e.g. seasonal variation, pollution levels.

The study includes patient records from January 1997 to December 2010. This study period was selected due to the availability and the quality of the data. The CPRD data for this study were extracted in December 2011, so data was available up to this date from 1988, but there were only a limited number of practices included in the data during these earliest years. Therefore the older CPRD data is less complete and changes in treatments, available medicines and practices have been introduced over time may make conclusions drawn from this data less relevant to current

practice. The linked HES data dates from 1st April 1997 until 31st October 2011. Therefore, the study duration was also restricted by the availability of the HES data to enable exacerbations that were treated within secondary care to be identified.

3.4.2 Selecting the study population

The study included asthma patients aged between 12 and 65 years who had received at least one ICS prescription within each calendar year, and who did not have COPD. Only patient with records that were recorded as 'up to standard' in the CPRD database were included in the study.

To select the patients to be extracted from the CPRD, the study cohort was identified using the term 'asthma' and ICS use using the CPRD GOLD online 'define' tools. Read codes (Appendix 6) related to asthma were searched for in the *clinical*, *referral* and *consultation* files in the CPRD using the built in the *medical* browser. Product codes (Appendix 7) related to ICS prescriptions during the study period were also identified by searching the *therapeutic* file using the built in product-search tool. These codes were combined together with the study period criteria i.e. a record during the registration period (1st Jan 1997 to 31st Dec 2010) using the online define tool to create a list of patients who had asthma and had been prescribed at least one ICS during this time period (Appendix 8).

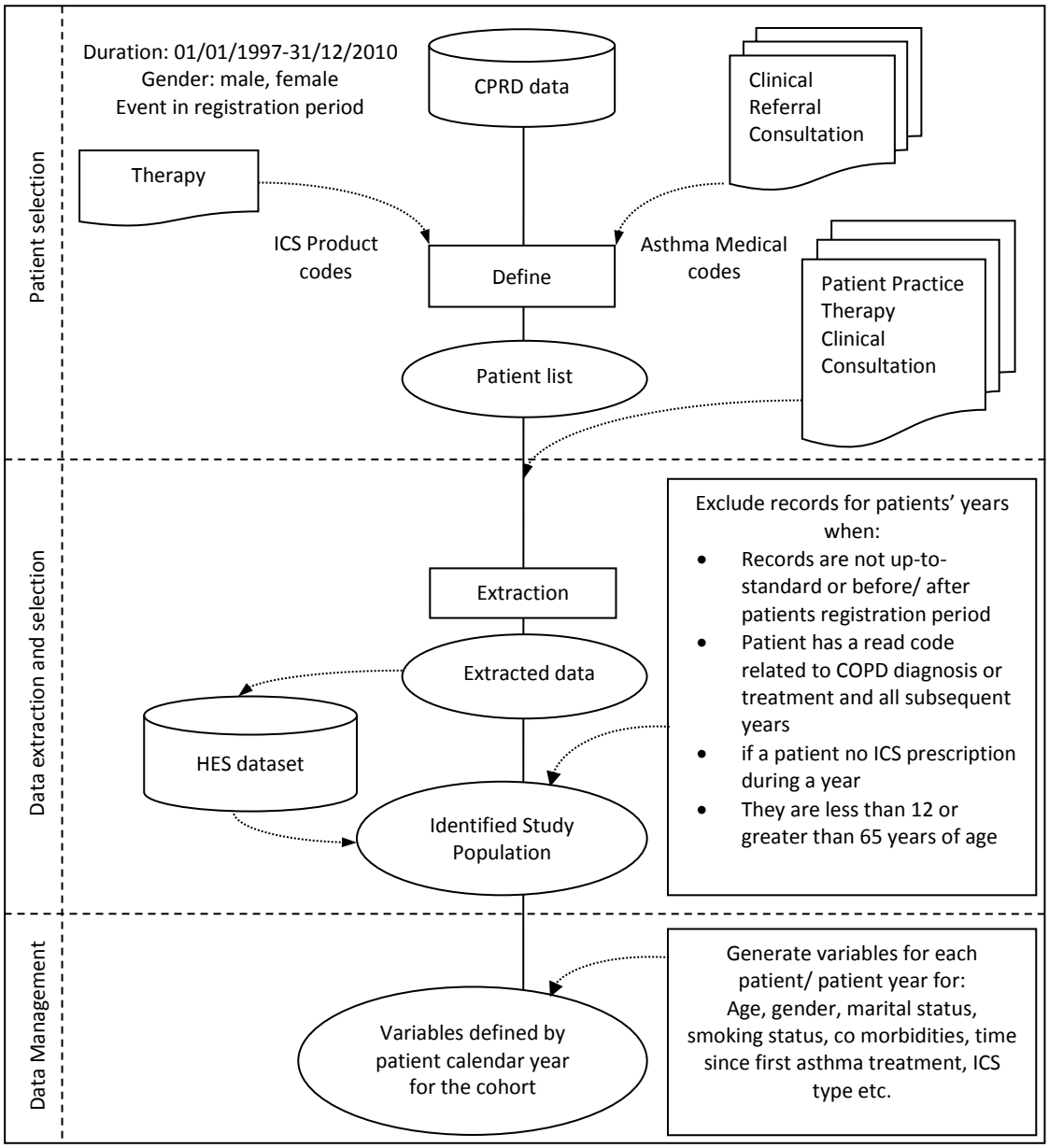
Eligible CPRD patients' records (based on the defined patient list) were then extracted from the *patient, practice, staff, referral, test, clinical, consultation and therapy* and *additional* files from the CPRD GOLD online database, using the CPRD 'extraction tool' based on the patient identifiers contained in the selected 'patient

list' and then further selection criteria were used to define the study cohort (Figure 3-1).

To ensure the quality of the data included in the analysis, all patients records dated before the practice *up to standard date* were excluded from the study. In addition, all patient records before the patients *current registration date* and any years after the patients *transfer out date*, were also excluded.

All patients were followed from the index date to the end of the follow up. The index date was defined as when a patient entered the study; either the start date of the study period (1st January 1997) or the start of the year when the patient first met the inclusion criteria. The end of follow up date was the date patients exited the study; either the study end date (31st December 2010), or before the start of the year when patients no longer met all of the inclusion criteria. Some patients may re-enter the cohort if they again met the criteria. Patients were only included for the calendar years when they met the inclusion criteria. For each patient, the time variant study variables were measured repeatedly over each calendar year between 1997 and 2010 for the years that they met the inclusion criteria.

Figure 3-1. Cohort selection and data extraction process in this study



3.4.2.1 HES data linkage

Next, the patients who were treated within the HES consenting practices (a list of HES consenting practices is available from the CPRD) were identified by screening the last 3 digits of the patient identifier (refers to the practice id) and matching these practice ID's with the HES consenting list. Patients with practice ID's that did not match were excluded.

3.4.2.2 Identifying asthma patients

To be included in the analysis, the extracted asthma patients were identified using both a diagnosis code or another asthma related medical Read code (Appendix 6), and were then tested to check that they had also received an ICS product code (Appendix 7) for each year that they were to be included in the study.

ICS prescriptions were identified in the cohort's therapy data using the ICS product codes (Appendix 8). The number of ICS prescriptions for each patient in each calendar year for each patient were counted, and any patient with less than one ICS prescription was excluded from the analysis for that year. This was to enable patient adherence to ICS to be calculated for each year where they were included and to ensure that they were actually treated for asthma (at asthma treatment level 2 or above).

Either a diagnosis or a treatment code were used to ensure all asthma patients were identified, since the asthma diagnosis codes alone did not identify all patients with asthma since there are expected to be some patients with no recorded diagnosis codes, and yet have asthma management and treatment codes.

This study assumed that if no ICS was prescribed, that there was no intention by the prescriber, or no perceived need for the patient to take the medicine. However, there are several reasons why an asthma patient may have no ICS prescriptions recorded within a calendar year, including patients who may access their medicines from elsewhere, the patient may have no treatable symptoms during this time, or the patient may have extremely poor adherence to ICS.

3.4.2.3 Age range

To be included in the study for any year, the patients must be between 12 and 65 years old.

Patient's age (in years) was calculated for each study year by subtracting the year of the study (e.g., 2009) from the patient's birth year (e.g. 1980). Any years before the patient was 12 years old or when they were older than 65 years of age were excluded from the study data.

Patients under the age of 12 years were excluded from the study since the guideline [3] recommendations for the treatment of asthma are different for children aged under 12 years, which could affect the calculations for treatment step, outcome and adherence. Additionally, patients may still 'grow out' of their asthma, influenced by puberty especially in boys at around this age. [155] These patients may not represent the patients with a chronic condition and if included may have affected the conclusions of this study if their asthma was resolving.

Patients over 65 were also excluded for a number of reasons. In the elderly (defined by the World Health Organisation as a chronological age of 65 years) [156] adherence would be expected to be confounded by additional factors to those influencing adherence in the other age groups. These could include comorbidities, differences in pharmacodynamics and pharmacokinetics, cognitive and functional impairments and access to free prescriptions. Many of these factors cannot be measured in this type of retrospective study and, inclusion of these patients in a study with younger patients may bias the results or weaken any observations made.

Comorbidities, which are more common in elderly patients, are believed to effect adherence, [80] either positively since that have greater contact with a healthcare providers, or negatively since they have many other medicines to take. Medicine use in the elderly across conditions is expected to be higher than in other age groups which could also affect adherence to their asthma medicines. In developed countries, the elderly have been reported to consume approximately 50% of prescription drugs, but represent only 12-18% of the population in these countries. [157]

Adherence could also be adversely affected by cognitive and functional impairments. Elderly patients have been found to have poorer inhaler technique [158] which could mean that the elderly patient may not receive their medicine correctly.

3.4.2.4 COPD

Each patient year with at least one COPD record and all subsequent years for that patient were excluded.

To identify patient years with a COPD code, the patient records in the extracted '*Test*' and '*Clinical*' CPRD files were screened for the read codes to identify COPD including the term 'chronic pulmonary' or 'COPD', chronic bronchitis, emphysema, or chronic obstructive airway disease (listed in Appendix 9).

COPD and asthma have similar treatments; therefore coexisting COPD would confound judgement about identifying treatments for asthma. Previous asthma adherence studies have also excluded patients with COPD [76] or excluded older patients (over 40-45 years of age) since this increases the likelihood of COPD,

especially in smokers. [103 159] Patients over the age of 45 were not excluded from this study, but smoking history was considered for all patients in the analysis.

3.4.3 Deriving the study variables

This chapter explores a variety of variables that may be associated with the adherence to ICS in asthma patients (identified in Chapter 2). The CPRD data was used to derive appropriate variables (Table 3-3).

The variables were identified in the study data by searching the Medcodes for Read codes and key words. Some of the variables were time independent, and recorded as the same value for every calendar year for a patient, but others were time dependent variables, where a value was generated and recorded against each patient year number.

Table 3-3. Variables for patient variables recorded in the CPRD

	Variable	Method used	Time dep	CPRD file	CPRD Variables	Categories	
Patient related	**Age**	The age of the patient for each year	✓	Patient	Year of birth (yob)	1:>=12 to <19	4:>=36 to -<45
						2:>=20< to 25	5:>=46 to <55
						3:>=26< to 35	6:>=56 to -<65
	Gender	CPRD recorded	X	Patient	Gender	Male or female	
	Marital Status	CPRD recorded	X	Patient	Marital	0=No data	9=Remarried
						1=Single	10=Stable
						2=Married	11=Civil Partnership
						3=Widowed	A grouped variable:
						4=Divorced	1= married/ remarried
						5=Separated	2=widowed, divorced/ separated
						6=Unknown	
						7=Engaged	3= single
						8=Co-habiting	4= cohabiting/ stable
	Region of living	Based on the Strategic Health Authority where the patient is registered	X	Practice	Region	0=No data	7=South West
						1=North East	8=South Central
						2=North West	9=London
						3=Yorkshire	10=South East Coast
						4=E. Midlands	11=N. Ireland
						5=W. Midlands	12=Scotland
						6=East England	13=Wales
	Smoking Status	Based on smoking status recorded	✓	Referral clinical	Appendix 11	0= non-smoker	By dummy variable:
						1= smoker	0= non-smoker
						2= ex-smoke	1= ever smoked
						3= passive	
	Comorbidities	The patient's Charlson comorbidity score	X	Clinical test	Appendix 10	Scored from 1- 18	
	Pregnancy status	CPRD recorded (record any time during the year)	✓	Clinical	Appendix 12	1=pregnancy	
						0= no record	
	BMI	BMI recorded or manually calculated using weight and height	✓	Test	Appendix 13	underweight=0, ideal=1 or overweight=2	
SES	**Prescription charge**	CPRD recorded	X	Patient	pressc	Exempt or not exempt	
	SES	Index of Multiple Deprivation (IMD) for patient and practice	X	SES		1= least deprived, 5=most deprived	
Condition	**Severity of Asthma**	By the BTS/ SIGN guideline treatment steps	✓	n/a	Chapter 5	Recorded as step 2 to 5 (set as 1-4 representing 2-5)	
	Severity Change	A change in the step by the BTS/ SIGN guideline	✓	n/a	Chapter 5	+ or – the number of steps from the previous year	
	Control of asthma	By SABA use, defined by the 2014 BTS/ sign guidelines [56]	✓	n/a	Chapter 5	0= patient has received prescriptions for under 10 SABA per day	
						1=patient has received prescriptions for 10 or more SABA per day	
	Clinical outcome	The number of asthma exacerbations treated within primary or secondary care	✓	n/a	Chapter 5	1= patient treated for at least one for an asthma exacerbation in the year	
	Duration of treatment	The number of years: since patient met the study inclusion criteria	✓	Therapy	n/a	Number of years	
Therapy	**Adverse effects**	An variable for each adverse effect for each year	✓	Clinical	Appendix 14	1= experienced oral thrush, osteoporosis or adrenal suppression during the year	
	Drug substance	A dummy variable for each drug substance prescribed.	✓	Therapy	Appendix 8	beclometasone, budesonide, ciclesonide, mometasone, fluticasone	
	Adherence	PPR, measured in the same/ previous year.	✓		Chapter 4	0-100%	

3.4.3.1 Time independent variables directly recorded in CPRD

Gender, marital status and region of living and prescription charge exemption are included as separate variables in the CPRD patient file, practice file. A variable was created for each patient for each of these variables, using the data directly from the CPRD. Labels were then attached to each value, using the CPRD look up files to decode the variables.

The socioeconomic status was included in a separate file. The comorbidity status for patients was calculated using the Charlson Comorbidity Index (CCI).

Socioeconomic status

There are 4 commonly used methods to measure comorbidity that are considered to be valid and reliable; the Charlson Index, the Cumulative Illness Rating Scale (CIRS), the Index of Coexisting Disease (ICED) and the Kaplan Index. [160] The Kaplan index was developed for diabetes research, and the CIRS does not consider specific disease diagnosis. The ICED considers both disease severity (mortality) and disability The Charlson Index is generally used to study mortality, but is the most extensively studied commonly used method to create a summary measure of comorbidity. [160]

The Index of Multiple Deprivation (IMD) was chosen to measure the socioeconomic status for this study, using quintiles version of the patient level data. The IMD is derived from of a number of indicators covering different aspects of material deprivation such as housing, employment, income, access to services, education and skills, crime, and living environment, [161] most recently updated in 2010 by the British Governments Department for Communities and Local Government.

Socioeconomic status by IMD is calculated at lower super output area (LSOA). [9] The LSOA is an area with a minimum size of 1,000 residents and 400 households. The LSOAs are built up from about 4-6 smaller Output Areas (OA), each containing approximately 110-140 households built from postcode units. [10] The CPRD map both the practice postcode and the patients home postcode to the lower super output area (LSOA), which is then linked with the 2007 English Index of Multiple Deprivation (IMD) for approximately 50% of the total CPRD patient population.

Each LSOA was classified into quintiles (five equally sized populations) by deprivation level where the least deprived patients or practices were classified as 1, up to 5; alternatives are 10 or 20 equal groups, all with the highest value representing the most deprived group depending on the number of groups used. Using the IMD data from the CPRD, a variable was created for each patient in the cohort.

Comorbidities

There are 4 methods of measuring comorbidity that are considered to be valid and reliable; the Charlson Index, the Cumulative Illness Rating Scale (CIRS), the Index of Coexisting Disease (ICED) and the Kaplan Index. [160] The Kaplan index was developed for diabetes research, and the CIRS does not consider specific disease diagnosis. The ICED considers both disease severity (mortality) and disability The Charlson Index is generally used to study mortality, but is the most extensively studied commonly used method to create a summary measure of comorbidity. [160] Therefore, the Charlson comorbidity index (CCI) [162 163] was chosen to measure patient comorbidity status in this study at baseline. CCI is a This index is a sum of the presence of 17

classes of diseases, weighted according to their association with 1-year all-cause mortality (Appendix 10), this is a validated method to predict patient mortality, but was used within this study to indicate the patients' health, which may influence adherence to ICS or asthma outcomes. Asthma is one of the conditions measured within the CCI, so all patients in this study cohort should have at least one condition identified in their CPRD records.

To calculate the Charlson comorbidity score, ICD-9 codes are used (the ninth revision of the International disease classification, published by the World Health organisation). In a study by Khan *et al*., ICD9 codes were translated into a list of Read codes that could be used to identify these same comorbidities using the CPRD data. [164]

The Read codes were identified in the *clinical*, *referral* and *consultation* files in the CPRD during the year when the patient was first included in the study period and a dummy variable was created to indicate whether a read code for each condition was present or not. When comorbidity was present, the dummy variable was set to equal 1. For each comorbidity, the dummy variable was multiplied by the assigned index value (weighting) and these added up to form a total score for the year for each patient.

3.4.3.2 Time dependent variables recorded in CPRD

For the variables that may change over time including smoking status, pregnancy, body mass index, signs of adverse effects caused by the ICS drug substance or oral steroids prescribed, a variable was created for each year, for each patient.

Age of patients in each calendar year

The age of a patient (in each year) was calculated for each patient year that they were included in the cohort, by subtracting the year of interest (e.g. 2009) from the patient's birth year (e.g. 1980).

Smoking status

For each year that the patient was included in the cohort, any smoking related Read codes recorded in the *referral* and the *clinical* CPRD files were identified using the key words smoke, smoked, smokes, smoking (codes are listed in Appendix 11). These records were categorised to create a set of variable for the smoking status for the patient year; smoker, non-smoker, ex-smoker, mother smokes and passive smoker. If a patient year had both a 'smoker 'and a 'non-smoker' code assigned within an individual year, the status was recorded as a 'smoker' for that year.

A dummy variable for whether the patient had ever smoked was also generated, assigning a 1 for a patient in any with a smoking record and any subsequent years. Where there were no records for an individual patient year, the result was recorded as a missing value.

Pregnancy

Patient records in the *Clinical* CPRD file with a Read code to indicate a pregnancy were identified using the key words; pregnant, pregnancy, maternity, antenatal. The identified codes were checked to exclude any codes that did not indicate pregnancy (Appendix 12). A dummy variable was created for each year to indicate whether the patient had a pregnancy record at any time during that year.

Body mass index

Patient records with a Read codes including key words for body mass index (BMI), weight or height were identified in the *Test* CPRD file (Appendix 13). Where the BMI was recorded, this value could be directly used. For any patient where both the height and weight was recorded, the BMI could be calculated. The greatest height ever recorded for each patient was used and the BMI was calculated for each weight measurement identified using the following BMI calculation and recorded in the new BMI variable.

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2} \qquad \text{Equation 3.1}$$

All outlying BMI records either below 10 or above 100 were not used as these would be expected to be caused by a recording or measurement error in the weight or height variable and the data was left as missing.

Signs of adverse effects from ICS /oral steroids

Patient records with a Read code for each adverse effect of ICS for candidiasis of the mouth, adrenal suppression or osteoporosis (Appendix 14) were identified using the key words adrenal or insufficiency, thrush, osteoporosis. The codes were identified in the *Test* and *Clinical* CPRD files and reviewed to check appropriateness. The records were summarised to create a dummy variable to indicate the presence of each condition for each adverse condition for each patient year.

Drug substance of inhaled corticosteroids

Prescriptions for ICS recorded for patients within the study cohort were identified using the prodcodes listed in Appendix 8, and categorised by drug substance. For

each patient year, the ICS prescriptions prescribed to each patient were summarised to create a dummy variable for each drug substance.

Time since the patient entered the study

A variable to indicate the number of years that each patient had been included in the study period for each patient was created, to show the progression of treatment over time by creating a count variable for each patient by year.

3.4.4 Data analysis

Descriptive statistics were used to describe the characteristics of the cohort and to summarise the characteristics of each variable and the characteristics were compared with national figures. Variables to represent the patient variables were presented in a cross-sectional tables and figures, and sub grouped by gender, since the asthma rates between genders are known to differ.

The annual prevalence of asthma patients in the study cohort was derived by dividing, the total number of patients per year by the number of eligible patients, i.e. the number of patients recorded in the CPRD data(during 1997 and 2010), aged 12 to 65 years, and were treated within HES consenting practices.

The incidence for oral thrush and osteoporosis were calculated (for each calendar year of the study period) by dividing the number of patients with new codes for the condition by the number of patients within the cohort for that year.

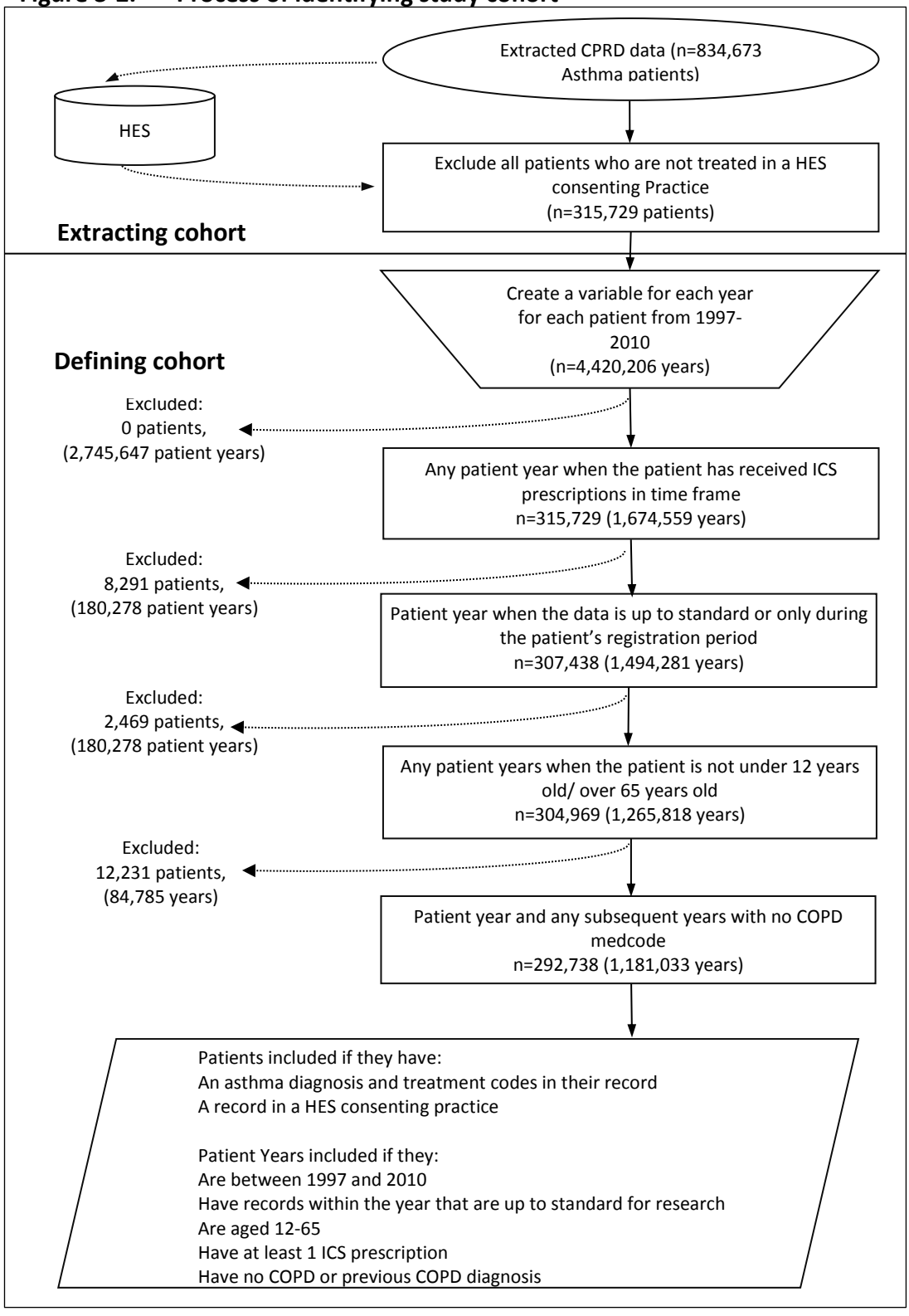
3.5 Results

3.5.1 Identification of the study population

Of the 635 practices (n=834,678 patients) in the extracted CPRD data, 224 (35%) of the practices (n=315,729 patients) had linked HES data.

A total of 292738 asthma patients met the inclusion criteria for the study (Figure 3-2) and account for 1,181,033 patient follow-up years. The median follow-up was 3 years (interquartile range: 1-6 years). The number of patients who met the inclusion criteria for the study (292,738 asthma patients) is 5.4% of the estimated eligible CPRD population in 2010 (5,318,647 patients).

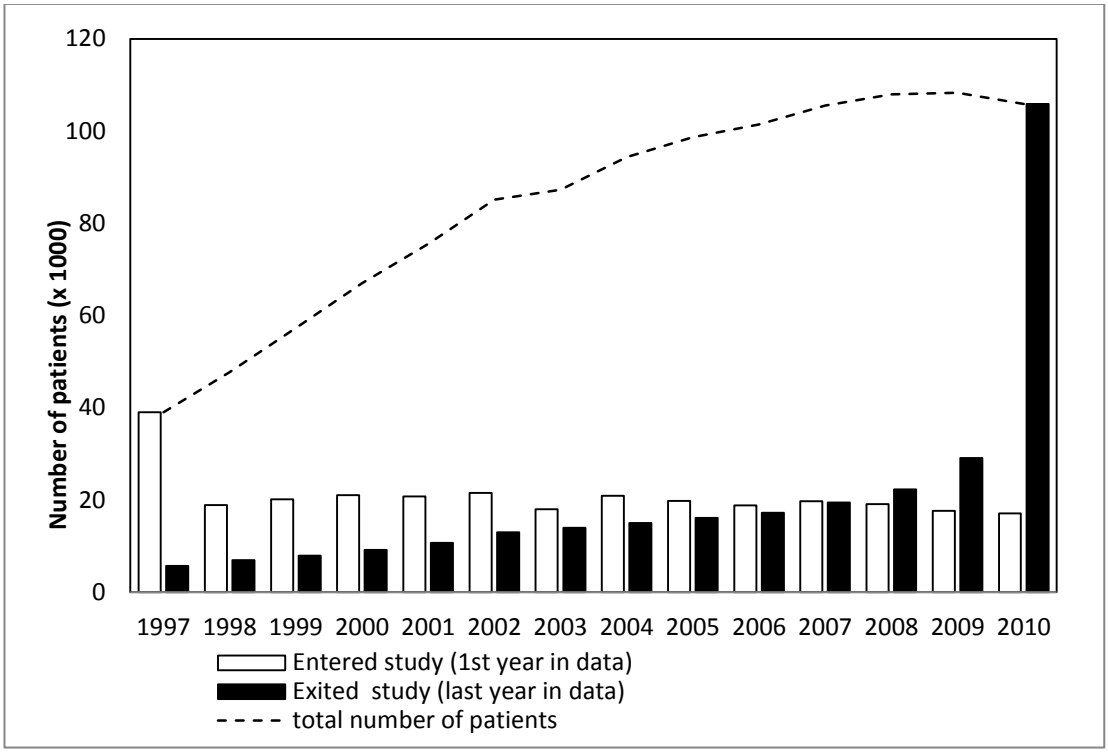
Figure 3-2. Process of identifying study cohort



As expected, a large number of patients entered the study in 1997 and a large number of patients left the study at the end of 2010 (the end of the study period). The total number of patients exiting the study each year increased over time, but

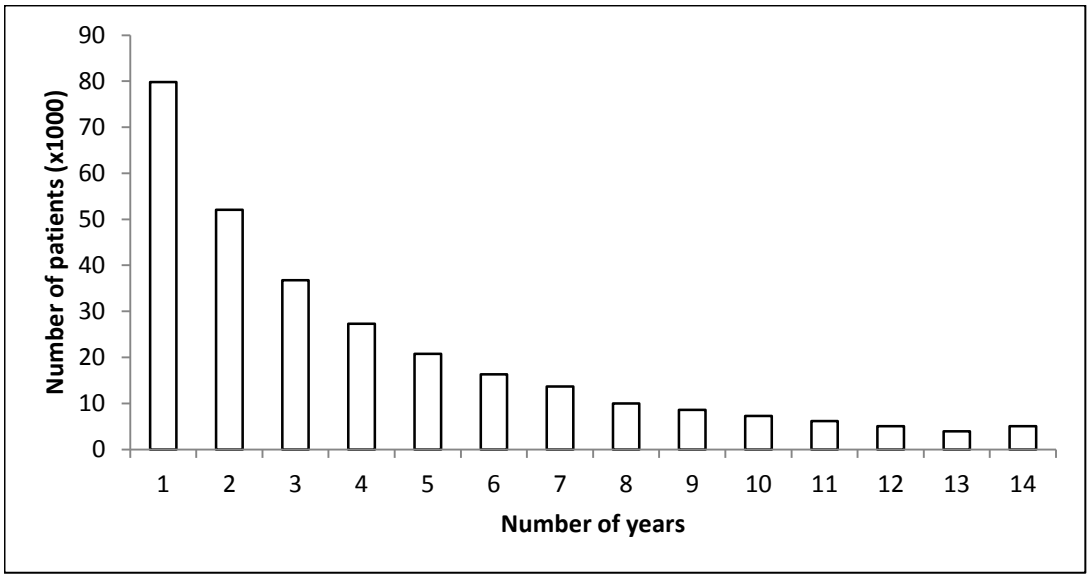
the total number of patients entering each year remained almost constant (Figure 3-3). The reason that these patients who left the study before the final year of the study period (74.1% of all patients in the cohort), were because they died (2.1%), left the practice (32.5%) or no longer met the cohort inclusion criteria (39.5%).

Figure 3-3. Number of patients who entered and exited the study in each calendar year



A total of 79,821 patients (27.3% of eligible patients) had only 1 year of data where they received an asthma prescription and 52,041 patients (17.8%) had only 2 years of data where they received an asthma prescription (Figure 3-4). A total of 160874 patients (55.0% of the study cohort) had 3 or more years of data included in the study.

Figure 3-4. Number of patients with different total number of years available for the study analysis



3.5.2 Time independent characteristics of the study cohort

3.5.2.1 Demographics

The mean age of the cohort at entrance into the study was 34 years. Most patients (24.73%) entered the study at 12 years of age as soon as they met the lowest age criteria for the study. The number of patients within each age band at entry into the cohort generally decreased when the age group increased. Previous literature has shown that the incidence rates of asthma were higher in children than in adults. [165] It is likely that patients who were diagnosed with asthma prior to their 12th birthday so were unlikely to be newly diagnosed at entry to the study.

A total of 56% of the selected cohort of 292,739 patients were female. When compared with the female population in England, the study cohort has a slightly higher proportion of female asthma patients than the national figure of 51.3%. [166] However, the proportion of females in the study is lower than the gender ratio of 18:26 males to females for patients who had an asthma diagnosis and were

prescribed a corticosteroid, reported by the Department of Health in the 2001 Health Survey for England. [167]

The proportion of asthma patients who met the study criteria was not consistently spread across the regions of the UK but the male to female distribution was similar within each region.

Comparing the population of each region against the published by the Office for National Statistics in 2010, [168] the number of cohort patients treated with in each region were not proportional to the population distribution of the UK. This difference may be due to different rates of asthma prevalence, diagnosis or treatment or the distribution of the practices that provide data to the CPRD.

The marital status for patients was not well recorded, where it was recorded (21.17% of patients) it appeared to be categorised mainly into two categories, i.e. married (53.98%) or single (36.87%). The nationally figure for the UK population is slightly lower for married (46.6%) and single (34.6%), [166] but this data is for the general population, and not specifically for asthma patients.

The proportion of patients with a recorded prescription charge exemption was only 1.5 % where slightly more females (1.74%) than males (1.24%) were exempt (Table 3-4).

Table 3-4. Characteriatics of the study cohort by gender, age at entry, marital status and region and prescription exemption

Variable	Category	Number of patients (%)	Male	Female
Age at Entry	12-20 years	72397 (24.73)	37613(29.19)	34784 (21.23)
	21-30 years	57336(19.59)	23603(18.32)	33733 (20.58)
	31-40 years	60151(20.55)	26231 (20.36)	33920 (20.70)
	41-50 years	47246(14.95)	19268 (14.95)	27978 (17.07)
	51-60 years	38603(11.83)	15240 (11.83)	23363 (14.26)
	60-65 years	17002(18.36)	6905 (18.36)	10097 (29.03)
Gender		292735	128860 (44.02)	163875 (55.98)
Marital Status	Single	23995 (8.20)	10895 (8.45)	13100 (7.99)
	Married	32420 (11.07)	9362 (7.27)	23058 (14.07)
	Widowed	628 (0.21)	104 (0.08)	524 (0.32)
	Divorced	2203 (0.75)	556(0.43)	1647 (1.01)
	Separated	828 (0.28)	244 (0.19)	584 (0.36)
	Engaged	62 (0.02)	28 (0.02)	34 (0.02)
	Co-habiting	1467 (0.50)	729 (0.57)	738 (0.45)
	Remarried	220 (0.08)	29 (0.02)	191 (0.12)
	Stable relationship	116 (0.04)	51 (0.04)	65 (0.04)
	Civil Partnership	14 (0.00)	5 (0.00)	9 (0.01)
	Missing	230782 (78.83)	106857 (82.92)	123925 (75.62)
Region	North East	5727 (1.96)	2534 (1.97)	3193 (1.95)
	North West	48472 (16.56)	21331 (16.55)	27141 (16.56)
	Yorkshire & the Humber	14217 (4.86)	6319 (4.90)	7898 (4.82)
	East Midlands	11053 (3.78)	4771 (3.70)	6282 (3.83)
	West Midlands	33936 (11.59)	15098 (11.72)	18838 (11.50)
	East of England	39247 (13.41)	17417 (13.52)	21828 (13.32)
	South West	35793 (12.23)	15633 (12.13)	20159 (12.30)
	South Central	37903 (12.95)	16741 (12.99)	21162 (12.91)
	London	37372 (12.77)	16232 (12.60)	21140 (12.90)
	South East Coast	29018 (9.91)	12784 (9.92)	16234 (9.91)
Prescription exemption	Exempt	4470 (1.51)	1613 (1.24)	2857 (1.74)
	Not exempt	448 (0.15)	204 (0.16)	244 (0.15)
	Missing	287817 (98)	127043 (99)	160774 (98)

The socioeconomic status record was missing for only 2175 patients (0.74%). There was a slightly higher proportion of the patients in the study who lived in an area with lower deprivation than in areas with high deprivation (Table 3-5).

Table 3-5. Characteriatics of the study cohort by quintiles of socioeconomic status

Quintile	Number of patients	%
1 (lowest deprivation)	64,936	22.35
2	64,487	22.19
3	56,543	19.46
4	58,566	20.16
5 (highest deprivation)	46,028	15.84
Total	290,560	100

The CCI was measured for all patients. A total 53,078 patients (18.14%) had at least one condition recorded, meaning that they had a condition diagnosed in addition to their asthma.

A total of 85.02% patients (n=248,870) of the study cohort had a CCI of at least 1, but 14.98% of patients (n=43,865) had a score of 0. These patients with a score of 0 did not have a specific asthma related diagnosis code included in their record despite being included in the cohort because they were treated for asthma with an ICS and also had an asthma treatment code (Table 3-6).

Table 3-6. Characteristics of the study cohort by charlson comorbidity score

Comorbidity score	Number of Patients	Patients (%)
0	43,865	14.98
1	195,792	66.88
2	15,427	5.27
3	28,016	9.57
4	5,297	1.81
5	1,877	0.64
6	1,191	0.41
7	463	0.16
8	285	0.1
9	367	0.13
10 and over	155	0.05

3.5.3 Time dependent characteristics of the study cohort

Only approximately 3.2% of patients (9253 patients) and 16.3% of patient years (192493 years) had a BMI recorded, or had a weight and height record to enable a BMI to be calculated. BMI was often recorded when patients were overweight (63.89% of the recorded values).

A pregnancy was recorded in 2.35% of all the years included in the study for females. The percentage of females who had a pregnancy somewhere within their record was 7.23%.

A smoking status was recorded in 645282 patient years (54.7%) and 173464 patients (57.9%) had at least one year with at least 1 record with a smoking status.

Approximately 42% of the smoking statuses recorded by year were recorded as a non-smoker.

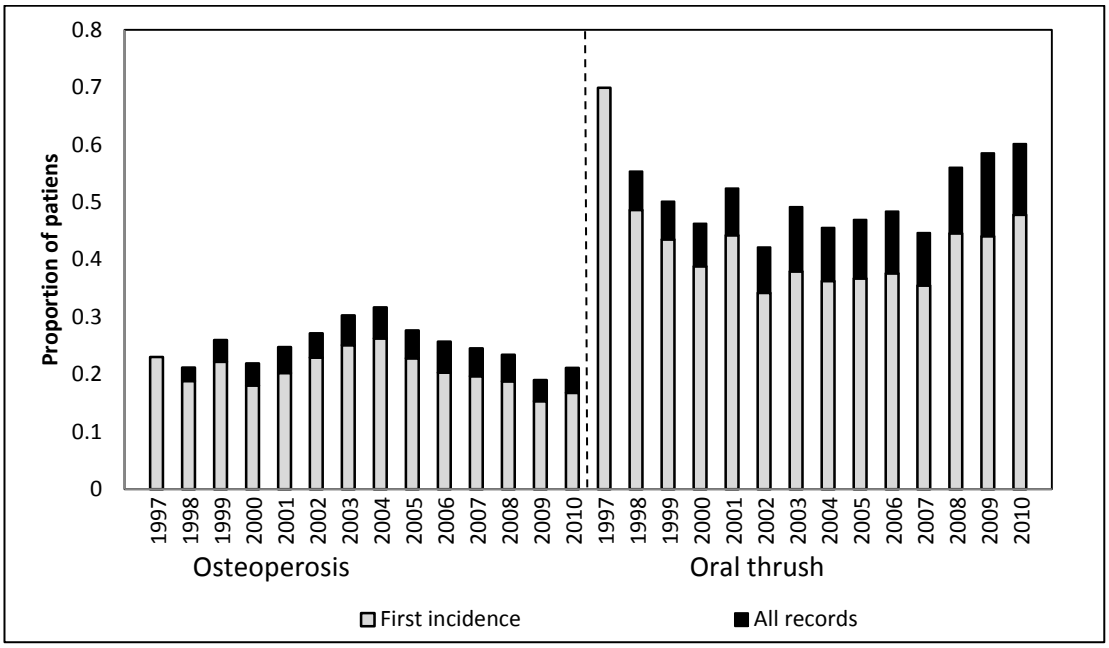
When the smoking status data was instead viewed per patient, approximately 55% of patients with a smoking status recorded were recorded as 'been exposed' to smoke, either by smoking themselves or by being exposed to passive smoke, leaving 45% with no smoking exposure. This proportion of smokers is similar to the proportion of adults in the general population who have either never or only occasionally smoked has been reported by the HSCIC in 2011 to increase from 43% to 53% between 1982 and 2009 [169] (Table 3-7).

Table 3-7. Characteriatics of the study cohort by pregnancy status, BMI and smoking status

Variable	Category	Total	Male	Female
BMI	**Underweight (<18.5)**	7094 (0.60)	3248 (0.63)	3846 (0.58)
	Ideal (18.5-25)	62411 (5.28)	20552 (4.01)	41859 (6.26)
	Overweight (>25)	122988 (10.41)	44069 (8.60)	78919 (11.81)
	missing	988530 (83.70)	444654 (86.76)	543876 (81.36)
Smoking Status	**Smoker**	259159 (21.94)	102431 (19.99)	156728(23.44)
	Non smoker	269912 (22.85)	113211 (22.09)	156701 (23.44)
	Ex-smoker	116195 (9.84)	52618 (10.27)	63577 (9.51)
	Passive smoker	1016 (0.09)	452 (0.09)	564 (0.08)
	missing	534741 (45.28)	243811 (45.57)	290930 (43.52)
Pregnancy status	**Not pregnant**	1165333 (98.67)	n/a	652810 (97.65)
	Pregnant	15690 (1.33)	n/a	15690 (2.35)

Overall 4893 patients (1.67%) were found to have a record for oral thrush, and 2429 patients (0.83%) had a record for osteoporosis. The numbers of patients with a newly recorded oral thrush or osteoporosis over each patient year did not show a consistent trend, either for the incidence or the prevalence of these events (Figure 3-5).

Figure 3-5. Annual incidence and prevalence of oral thrush and osteoporiosis



When the drug substance prescribed was investigated, during the study period the majority of patients were prescribed belcometasone (63.90%). Some ICS's such as ciclesonide were only introduced to the market more recently, so were therefore only prescribed more frequently later in the study period (Table 3-8).

Table 3-8. Characteriatics of the patient years, where patients were prescribed different substance of ICS

ICS drug substance prescribed	Number of years (prescribed drug)	Number of patients (prescribed drug)
Belcometasone	794,843 (63.90%)	240704 (60.94)
Budesonide	176271 (14.17%)	68157 (17.26)
Ciclesonide	1543 (0.12%)	732 (0.19%)
Mometasone	1539 (0.12%)	832 (0.21%)
Fluticasone	269630 (21.68%)	84549(21.41%)

***The totals number of patient years summed across the different ICS will be greater than the number of patients and patient years in the study since some patients may be included in two categories in one year.**

3.6 Discussion

3.6.1 Suitability of the CPRD data set for the study and the study cohort

The preliminary investigations of the variables in the CPRD for the study cohort showed that a large sample size (292738 patients) and sufficiently large follow up period up to 14 years for individual patients (1181033 patient years in total) was available, identified from the CPRD using the inclusion and exclusion criteria. Two or more years of data were available for 72.5% of patients and three or more years of data were available for 45.0% of patients, which allowed trends in adherence over time to be observed. Therefore, the CPRD is a suitable data set for this purpose of this study.

The annual number of patients who entered the study is relatively consistent over time. Alongside this, an increase in the patients leaving the study was observed. Most patients 'left the study' because they moved practice or no longer met the

criteria, this could be because they reached their 65th birthday (the rate would increase in an aging population as seen in the UK [170]) or if their asthma improved so they no longer required an ICS to treat it. This increase in patients leaving the study did not result in a decrease in prevalence of asthma in the cohort because the incidence rate for each calendar year remained higher than the exit rate. The prevalence of asthma patients who were prescribed an ICS in the CPRD during the study period was calculated to be 5.4%.

In the 2001 Health Survey for England, 5.2 million people were reported to have asthma, [167] based on a population of 49.14 million in 2001 [171] this represents 10.58% of the population. The Health Survey for England in 2001 [167] also reported that, approximately 22% of patients with asthma were prescribed a corticosteroid. By combining these figures; an estimated prevalence of asthma patients who were also prescribed an ICS was 2.3%, this figure is slightly lower than the prevalence for the study cohort at 5.4%.

This minor difference in the measured asthma prevalence may due to different selection criteria for the study cohort. For example, not all patients are registered with an NHS GP; and patients who are not registered would not be expected to be able to be treated for their asthma but may appear to have asthma reported in the survey data. In addition, as the cohort included patients aged 12-65 years, but the Health survey included patients of all ages. The slight difference is unlikely to influence the study outcomes as this study focuses on the issue of adherence, which means that the cohort must only include the patients need to received treatments.

3.6.2 Strengths and limitations of the study variables

Many of the variables may affect adherence to ICS in asthma were able to be identified from the CPRD data. Although some variables were missing or could not be calculated, many were reasonably well recorded such as the patient's age, gender, ICS drug prescribed, and region. However, those variables which were either poorly recorded (such as BMI) need further cautious investigation or interpretation.

Some patient variables (marital status and prescription charge exemption) were recorded only once for each patient, since it is updated in the patients record rather that a new record added. This makes marital status reasonably unreliable, especially for older patients because only the recently recorded marital status is recorded. Similarly, for prescription charge exemption because a patient's exemption status (e.g. maternity exemption, under 16 year, over 60 years of age, receives income support etc.) could change over time.

The patients deprivation status was found to be reasonably complete and considered to also be reasonably accurate, despite being based on a status for an area and not a specific record for the patient. However, counter intuitively, patients who lived in the most deprived areas were found to have lower asthma prevalence. This may be explained by patients who live in deprived areas do not actively seek treatment from primary care as readily as patients with lower deprivation.

Approximately 16% of patients in the study cohort had a comorbidity score of 0, meaning that the comorbidity methodology used did not identify all of the patients in the cohort with asthma. In the cohort selection procedure, the inclusion criteria

of an ‘asthma’ term somewhere within the patients’ records (excluding suspected asthma or a family history of asthma) allowed patients to be included who did not have a specific asthma diagnosis code within their records, rather than only those patients with asthma diagnosis codes. This led to more patients being included in the cohort than would be included in an asthma registry, or when identified using the methodology by Khan *et al*. (2010) to identify asthma as one of the comorbidities. Ideally the same methodology would be used for both selections , however Khan’s method of identifying comorbidities has more validation than would be possible than one generated for this study alone despite missing some patients with asthma. Therefore, comorbidity score will sometimes underestimate the number of conditions that a patient had, however, the effect of this miss identification is expected to be low.

Patient BMI was very poorly recorded, with more records reporting that the patient is overweight than would be expected. Patients are more likely to be weighed (and the weight recorded) if there are concerns about their weight, but also may be because patients with asthma may be more overweight. This is difficult to test using this cohort of asthma patients. Where completed the BMI can be considered to be accurate, however, the included records may not be representative of the cohort.

Patients’ smoking status appears to be reasonably well recorded in the cohort. This was expected since there are QOF points available for having this information recorded for asthma patients. [42] However, a patient may have multiple entries for smoking status as their smoking status changes over time, or they may have their smoking status recorded again in a different year. Therefore a second smoking

variable was created to record the patient's status as whether they had ever smoked.

The date of diagnosis or start of treatment was not available for all patients in the cohort since some patients entered the study cohort after diagnosis, for example if they had moved practice, if the practices data became up to standard after the event or if the patient was diagnosed before the start of the study. Therefore, T_0 for patients was chosen to be the year when they first appeared in the study cohort; either the point of diagnosis or when they met the inclusion criteria for the study, usually when they reached 12 years old or when they started treatment with ICS or SABA. Therefore, specific conclusions cannot be made about points in treatment from diagnosis, e.g. identifying times at highest risk of poor adherence from diagnosis, but instead the patient year variable shows progression through treatment.

There are some variables that may be possible to measure using the CPRD data, but have not been included in this study. Many of these are too complex to extract as part of this study or are not complete enough to create a valid measure to use. These include: changes in treatment over time, complexity of treatment, interventions to improve adherence, adherence of prescribing to the guidelines, peak flow, number of prescribers and the number of appointments.

A variable for specific changes in treatment would be extremely complex to try to summarise the changes made into categories, since patients will move up and down treatment steps and may be treated with different medicines and doses at each step. Either an excessive number of categories would be required or the individual

categories would be too general. The treatment step variable to represent severity of asthma and the variable to signal a change in this treatment step derived in Chapter 5 represent a general treatment level and treatment changes.

Complexity of treatment, could be measured, for example by the number of medicines that a patient is prescribed however, again may be difficult to find a meaningful categorised measure, and is generally captured within the treatment step variable.

Interventions used to improve adherence do not appear to be consistently reported, since many different interventions may be used, by different heath care professionals such as within a pharmacy, which may not appear in the data. Therefore an intervention variable could not be included in the study.

In addition to the variables that were too complex, incomplete or inconsistent to be included in this study, some variables that may affect adherence or clinical outcome in asthma could not be measured using a retrospective database; these included a patient's cognitive function, the patient's beliefs about their medicines or their condition etc. This is a limitation of the study using the available data, but may be partially controlled for in the modelling in Chapter 7, by the inclusion of variables such as severity or exacerbation.

3.7 Conclusion

The study cohort selected from the CPRD (asthma patients aged 12 to 65 years with no COPD records and at least one ICS prescribed per year, and who had records linked to HES secondary care data) is a good representation of the asthma

population who are treated with ICS in the UK population. Where comparable, the prevalence in the study cohort showed similar characteristics to those that would be expected to be observed in the general population.

The study variables could be derived from the available CPRD data, and most were found to be reasonably complete for patients. The variables included the time independent variables (gender, region, and socioeconomic status) and the time dependent variables (comorbidities, pregnancy, adverse effects of ICS, and the prescribed ICS). The subgroups of these variables in the selected cohort were characterised to help to understand the meaning of each variable to aid in the interpretation of results including these variables later in the study.

Despite the limitations due to the retrospective nature of the study, making it necessary to fit the study variables to the data available, the variables that have been successfully derived can be used in the analysis alongside the variables derived for clinical outcome and severity of asthma, derived in Chapter 5, to investigate the effect of these variables on the adherence variable (derived in Chapter 4).

Chapter 4 Development and validation of the methodology used to measure adherence to inhaled corticosteroids using prescribing data

4.1 Introduction

The aim of the study was to investigate what characteristics are associated with a patient's adherence to ICS, and how these relationships may change over time. To measure the changes in adherence, adherence was measured over repeated intervals, creating a panel data structure. For this study an annual interval was chosen, as discussed in Section 3.4.1, by calendar year, which was also assigned a number to count the number of years since the patient entered the study described as the 'patient year'.

Asthma is a chronic condition, where ICS prescribing for asthma control is recommended for use on a daily basis, without gaps in treatment, as defined by the clinical guidance. [3] Therefore, for this study it is more important to focus on the proportion days where medicine was taken (adherence), rather than focusing on the proportion of days missed (medication gaps) or the duration of time until doses were missed (persistence). [98]

There are many methods that have previously been used to measure adherence using retrospective data, summarised in Table 2-3, the most commonly used methods are the MPR and the PDC. The difference between these 2 measures is that PDC excludes the double calculation of days when prescriptions overlap,[83] therefore, PDC cannot exceed 100%. In the UK, dispensing or medicine taking information is not generally available with linkage to other individual patient or

clinical information, except for some small scale local cohort studies. [107 118] Therefore an MPR cannot be calculated; however, retrospective primary care prescribing data, such as from the CPRD, is available, which is a rich source of data with the potential to be used to create a PPR as a proxy measure for adherence. PPR is similar to the established MPR adherence measure, but instead uses prescribing rather that prescription fill data for the calculation. Many previous retrospective adherence studies in asthma and across other diseases have used prescribing data to measure adherence, but it is often referred to as a MPR or as 'adherence', despite using prescribing data for the calculation. [104 105 107 172 173] The 2014 British asthma guidelines suggested that computer repeat prescribing systems provide a useful measure of compliance [56] and the 2016 guideline update [3] included a reference from this PhD study as evidence to support the use of computerised prescribing records to indicate adherence. [16] Mabotuwana *et al.*, 2009, found that for long-term medications PPR was reflective of the medicine possession ratio (MPR) using prescription fill data. Mabotuwana *et al*., calculated a PPR using prescribing data for treating long-term conditions and compared with an MPR calculated by using dispensing data. [101]

Currently, there are only a few studies that have used retrospective primary care data to measure adherence using prescribing data (Appendix 4). In addition, no studies were found to have measured adherence to ICS longitudinally using the CPRD data (Chapter 2). Furthermore, no studies have previously used cross-sectional measures of adherence over repeated calendar years to enable any changes in adherence to ICS in the treatment of asthma and the causes of these

changes to be investigated. Therefore the characteristics of asthma and ICS and the information that is available to be used from the CPRD data must be considered to select the most appropriate method for the definition and calculation of an adherence measure.

4.2 Aim and objectives

This chapter aimed to develop a proxy measure of adherence to ICS in asthma patients which can be used to measure cross-sectional adherence over consecutive calendar years for each patient in the cohort using the prescription data in the CPRD. The objectives included:

- To explore the different data management approaches for deriving the number of days' supply prescribed by each prescription.
- To explore the most appropriate approaches for calculating the numerator and the denominator of the PPR in each calendar year.
- To evaluate the adherence to ICS in the treatment of asthma using PPR defined in this study.

4.3 Data management

All ICS prescriptions issued to the study cohort (6,095,956 prescription records) were extracted from the CPRD data '*therapy*' file using ICS product codes (Appendix 8). Each prescription included information in eight variables; example data for 2 prescriptions were presented in Table 4-1.

To calculate the PPR for each patient year in the cohort, the number of days of ICS prescribed by each prescription was required The recorded 'number of days' supply variable for each prescription, was missing for 97.45% of prescriptions. The values

that were recorded were more commonly for lower quantities of medicine prescribed than would be expected even for patients with low adherence. Therefore, we would not expect this small proportion of the cohort with the 'number of days' recorded by the prescriber to be representative of the 'number of days' prescribed variable for the whole cohort. Therefore, appropriate data management strategies were required to impute the missing 'number of days prescribed' data, using information available from other variables including the 'number of doses prescribed' and the 'numerical daily dose'. However some of the values, for these variables were also missing, making further imputation steps necessary. The imputation process aimed to be as complete and accurate as possible, but to avoid causing bias to the results.

Table 4-1. Prescription information for the cohort contained in the CPRD therapy file with examples for two ICS prescriptions

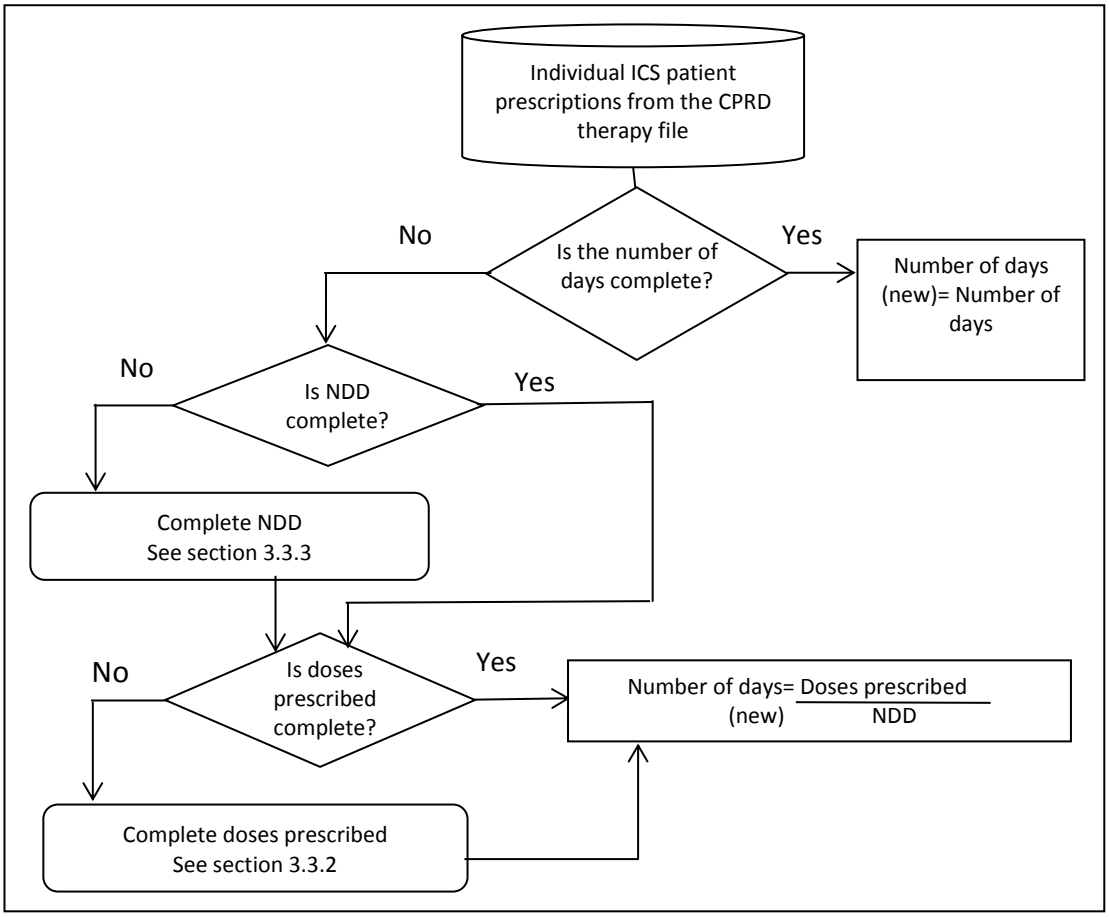
Variable	Description	Example 1	Example 2	Number of records	% of records missing
Patient number	The unique and anonymous patient identifier	5678	1234	6,095,956	0%
Event date	The date when the prescription was given to the patient	30 Dec 1999	12 June 2009	6,095,956	0%
Product code	A coded variable to record a product description including name, drug and strength	Budesonide 200 mcg	ALVESCO inhaler 160 mcg/ act	6,095,956	0%
Textid	A coded variable to record the NDD. Decoded using the 'Common Dosages 'look up file.	4	2	5,457,062	10.48%
NDD	The numerical daily dose recorded for the prescription	4	2	5,133,751	15.79%
Packtype	A coded variable corresponds to the pack size prescribed (also used to record some NDD values).	200	120	5,676,701	6.89%
number of packs	Number of packs prescribed	2	2	175,230	29.12%
Total Quantity	The total quantity of doses or the number of units/ packs prescribed	1	2	6,078,011	0.29%
Number of days	The number of days of medicine supply that the prescription should cover	50	60	155,612	97.45%

For each individual patient, some ICS prescriptions were also found to be recorded on the same day. For these prescriptions, the number of days prescribed by each prescription were summed to give a total number of days prescribed. However, duplicate prescription records on the same date (in terms of all variables in the 'Therapy' file) were deleted as these are assumed to be a duplicated record as a result of incorrect recording, making it inappropriate to add up the doses from these prescriptions.

4.3.1 Managing the missing number-of-days prescribed variable

The conceptual framework for managing missing 'number of days' supply variable is illustrated in Figure 4-1.

Figure 4-1. Approaches to impute missing information for the number of days prescribed variable



The first method used to impute any missing information for the 'number of days' prescribed, was by dividing the recorded *'number of doses'* prescribed, by the recorded 'numerical daily dose' (*NDD*) for each prescription. However, there was also missing information for NDD (15.79%) and 'number of doses prescribed' (0.29%) in some prescriptions. Therefore, several different data management procedures (Table 4-2) were also needed to impute the missing 'NDD' (section 4.3.2) and the 'number of doses prescribed' variables (section 4.3.3).

Table 4-2. Methods used to impute the missing doses prescribed and NDD variables in each prescription

Alternative variables	Description
Doses prescribed (A)	Use only the raw quantity x packsize values to calculate number of doses
Doses prescribed (B)	Use the rules to derive the number of doses prescribed (section 4.3.2)
NDD (A)	Use only the NDD values recorded
NDD (B)	Imputation for NDD based on past and future prescriptions (section 4.3.3)
NDD (C)	Imputation for NDD based on past and future prescriptions and based on dosage form (section 4.3.3)

The impact of these separate data management procedures (sections 4.3.2 and 4.3.3) on the resulting '*number of days prescribed*' variable, was investigated by firstly comparing the 'number of doses prescribed' derived from the two methods (doses prescribed A and B) as well as comparing the NDD results derived from the three methods (NDD A, B and C) using descriptive statistics.

Secondly, the 'number of days prescribed' by each prescription were calculated by using different combinations of data management approaches (Table 4-3) for the missing 'doses prescribed' and 'NDD'. The matrix created a total of seven alternative strategies and the completeness and the summary statistics (mean, inter-quartile range and the standard deviation) of the number of days prescribed were calculated for each strategy and compared.

Table 4-3. Alternative strategy to impute the missing values for the number of days prescribed

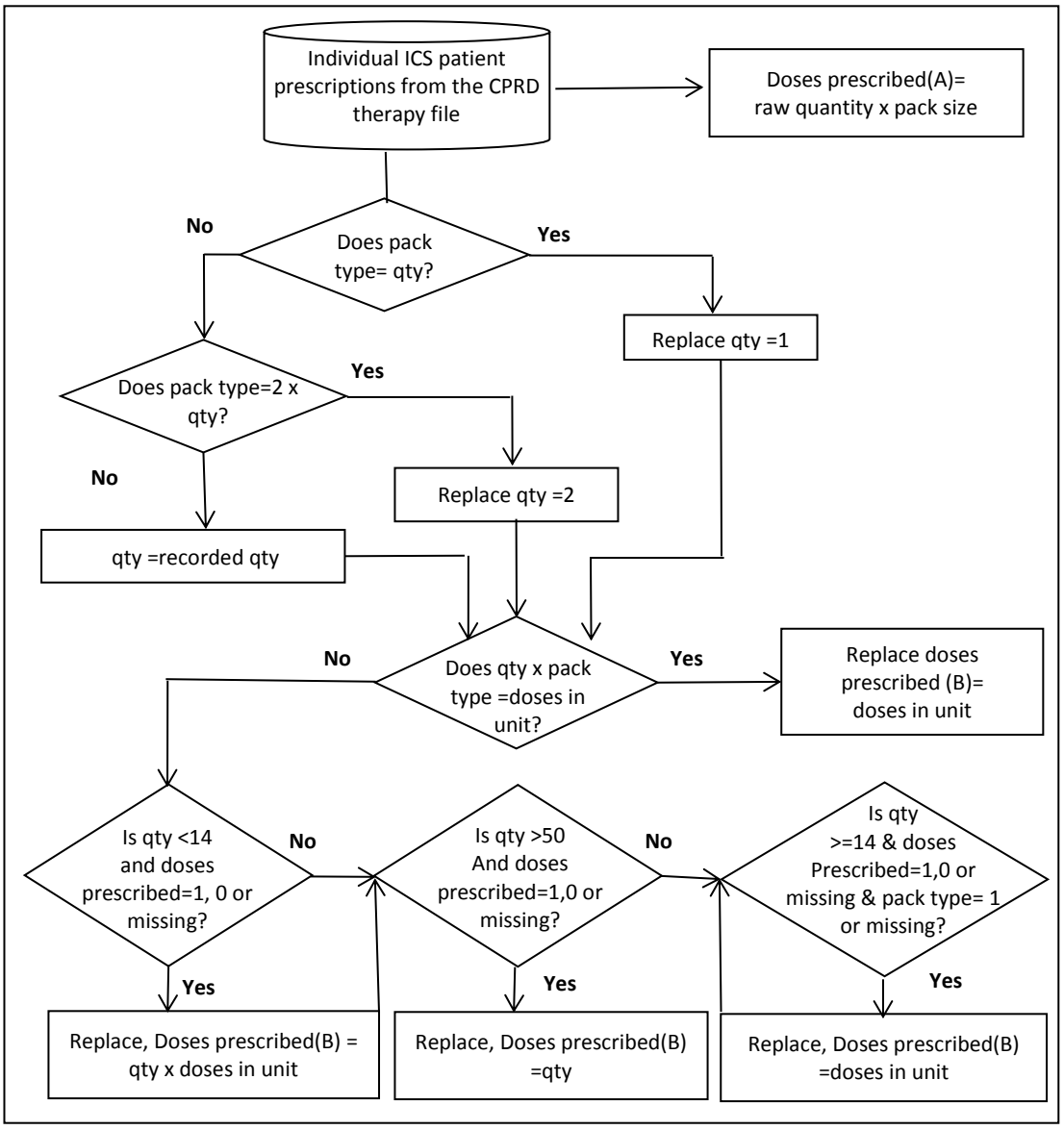
Data management strategy	Method for imputing number of doses prescribed	Method for imputing NDD
1	none	none
2	Doses prescribed (A)	NDD (A)
3	Doses prescribed (A)	NDD (B)
4	Doses prescribed (A)	NDD (C)
5	Doses prescribed (B)	NDD (A)
6	Doses prescribed (B)	NDD (B)
7	Doses prescribed (B)	NDD (C)

4.3.2 Managing the missing number-of-doses prescribed variable

To impute the missing values in the 'number of *doses prescribed*' variable the number of doses in a single unit/ pack (from the *'packtype'* variable) was multiplied by the number of units/ packs *('quantity'*) prescribed. However, these variables were also often found to be recorded inconsistently, e.g. the *'quantity'* variable was often record as number of doses rather than the number of units/ packs or were missing or unrealistically high or low (regarded as outliers).

To improve the completeness and quality of the data, a set of rules were used. *A*ny inappropriate or outlying data were identified and corrected using a series of steps to check the number of *'doses prescribed'* (Figure 4-2). A new variable for the number of 'doses in unit' was also created, by finding the most appropriate pack size information from the British National Formulary, [44] based on the recorded product code. This variable was used to replace outlying values where appropriate, and to check the other results.

Figure 4-2. Approaches to impute the missing information for the number of doses prescribed variable



4.3.3 Managing the missing numeric daily-dose variable

To impute the missing NDD values (692,205 values, 15.79%), information from the 'common dosages' text variable and the 'packtype' variables were used alongside some additional data management steps (Figure 4-3).

The packtype variable was checked for any information related to '*NDD'* and where available was used to replace the missing or outlying '*NDD'* variable.

The '*text ID*' field in the *therapy file* was used with the '*common dosages*' look up file to identify the NDD values for each of the prescriptions and used to impute any missing NDD value. If the NDD remained missing, it was sometimes recorded as 'free text' within the look up file, where possible this was manually translated into a numerical result for the NDD and the missing values were updated.

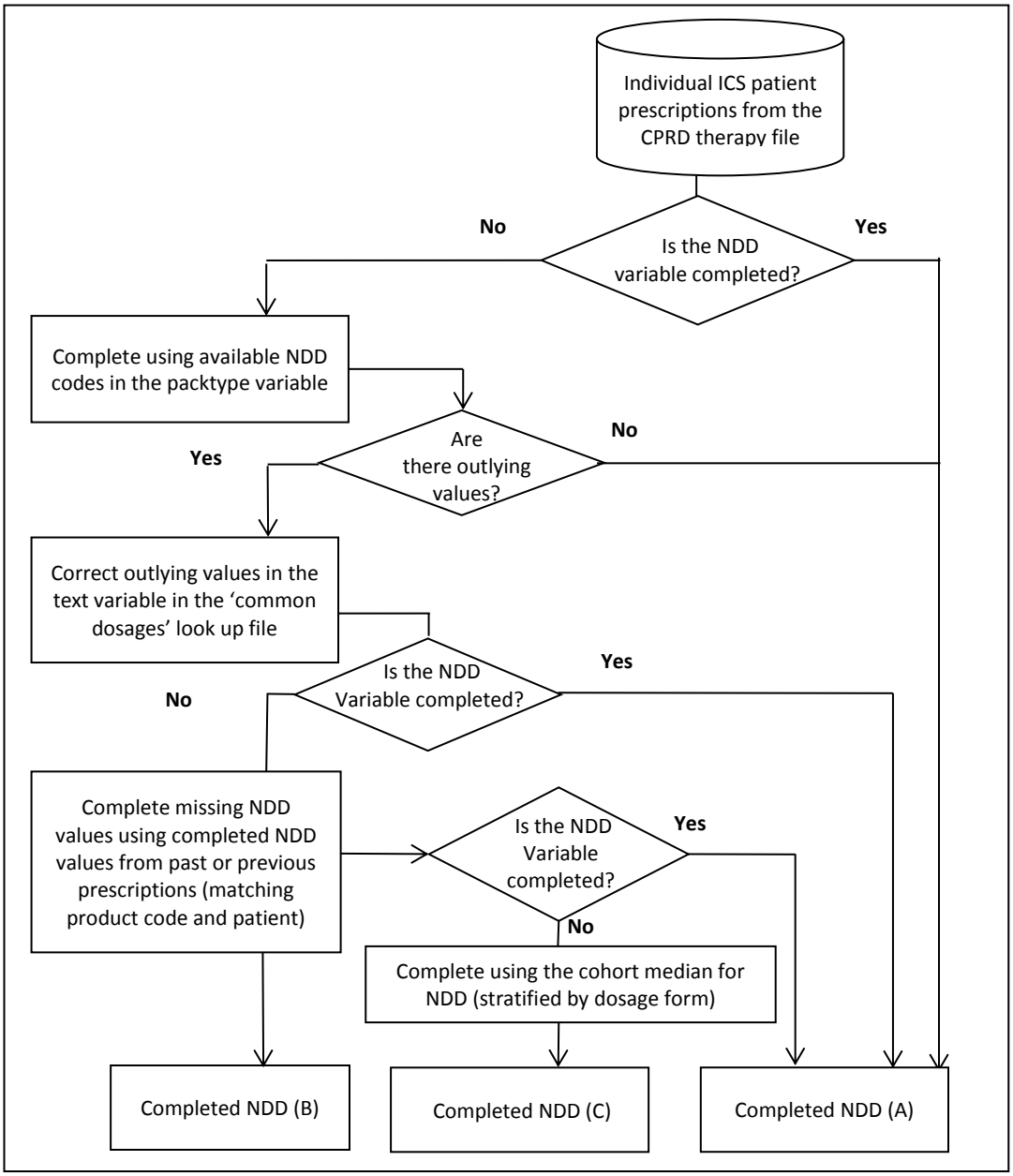
Any '*NDD'* that was greater or equal to 50 was assumed to be more likely to be a mass of medicine (dose in mg) to be taken rather than a number of doses recorded. In these cases, the '*NDD' was* corrected.

Any remaining missing values were then imputed by using any available previous or future prescriptions for the same patient and product or other prescriptions issued using a repeat prescription, within the previous or next 28 prescriptions. The choice of 28 prescriptions approximately represents around 2 years of prescribing if prescriptions were to cover 30 days. Two years was chosen as a compromise between replacing as many missing '*NDD'* values as appropriate, and using '*NDD'* from too far into the past or future when it is more likely to have changed. An assumption was used that the NDD is likely to be recorded in the data when it is changed.

Where missing values remained in the NDD variable, a further assumption was made based on the aggregated cohort for each dosage form of ICS i.e. metered dose inhaler (MDI) or breath actuated/ dry powder inhaler (DPI). The distribution of the NDD was investigated (Appendix 15) and the values of 2 daily doses for DPI and 4 for MDI are the most common NDD's prescribed within the data, this suggests

that an '*NDD'* of 2 was a reasonable assumption for the DPI prescriptions and an '*NDD'* of 4 was a reasonable assumption for the MDI prescriptions.

Figure 4-3. Approaches to impute missing values in the NDD variable



4.4 Developing the prescription possession ratio measure

The PPR for ICS was calculated by dividing the total number of days of a medicine prescribed to an individual patient within a one year time period, by the number of days in that time period.

$$\text{PPR} = \frac{\text{number of days of medicine prescribed}}{\text{number of days in the time period}} \times 100 \qquad \text{Equation 4.1}$$

The numerator and the denominator of the PPR calculation were derived using each of the four alternative methodologies to derive the numerator (section 4.4.1) and the two methods to determine the denominator (section 4.4.2). The methods were combined to create 5 different strategies to calculate the PPR for each patient calendar year. The results of PPR measured using these five strategies were then summarised and compared to select the most appropriate methods to be taken forward for further analysis (section 4.4.3).

The five methods (A to F) are described in Table 4-4, alongside the clinical implication that is made by each method in the context of taking ICS in the treatment of asthma.

Table 4-4. Clinical implications for the alternative methods to derive the numerator and denominator for the PPR calculation

Method	Description	Clinical implication
Method A	Including overlapping days prescribed between prescriptions	Remaining doses would be taken before the new prescription used
Method B	Not including overlapping days prescribed between prescriptions	Remaining doses would be discarded when a new prescription was issued.
Method C	Passing excess days prescribed to the next interval (year)	Doses would be taken as prescribed, followed by a period with no medicine (if under prescribed).
Method D	share excess days prescribed proportionally between intervals (years)	If under prescribed, patients would under dose daily, but take medicine for the prescription duration.
Method E	Interval duration (set at 365 days)	Patients only leave or enter the data at the year-ends.
Method F	Sum of the individual prescription intervals	Patients enter or leave the data pat way through a calendar year.

4.4.1 Deriving the numerator for PPR calculation

The numerator variable for annual PPR for ICS for an individual patient was the sum of the number of days prescribed across all ICS prescriptions over a given year. But alternative methods were identified to manage remaining medicine supply when a new prescription was recorded and led to overlapping of prescribed days, and where some of the doses that were prescribed prior to the start (or at end) of the annual interval, were intended to be used in the following year.

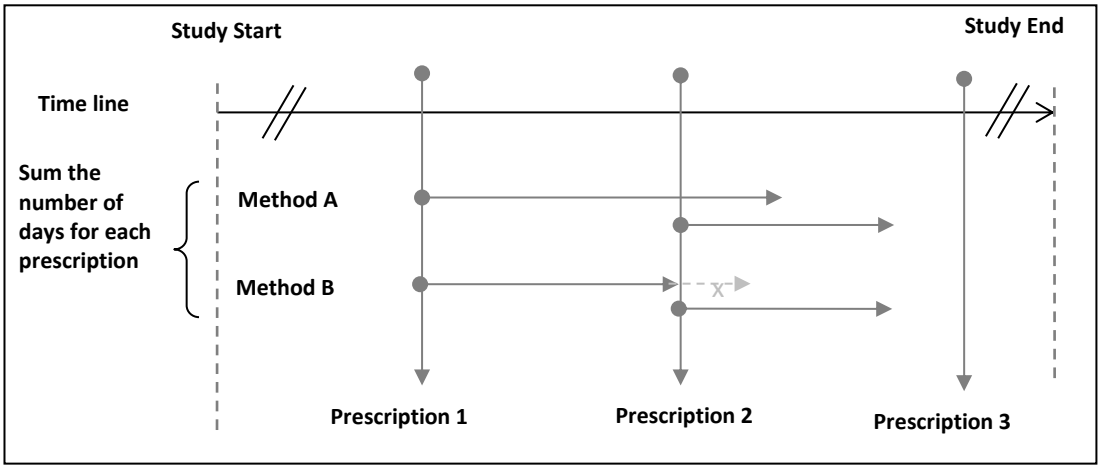
4.4.1.1 Overlapping prescribed days

The prescription days that remained when a new prescription was recorded can be included (method A) or excluded (method B) from the total days of ICS prescribed (Figure 4-4) calculated for the year.

In method A, the overlapping days were included in the calculation, the total number of days prescribed by each prescription during the year were summed together. Therefore, it was possible that the number of days of medicine prescribed in the interval could exceed the number of days for the interval.

In method B, the overlapping days were excluded, any days remaining from a prior ICS prescription that remained when a new prescription was recorded, were excluded from the sum of the total number of days of ICS prescribed during the year. Therefore the sum of the 'days prescribed' represents the days where medicine was available to the patient during the year. In the literature, this method was often referred to as the proportion of days covered (PDC). [83]

Figure 4-4. Two alternative methods for calculaing the sum of the number of days prescribed when prescription supply days overlap



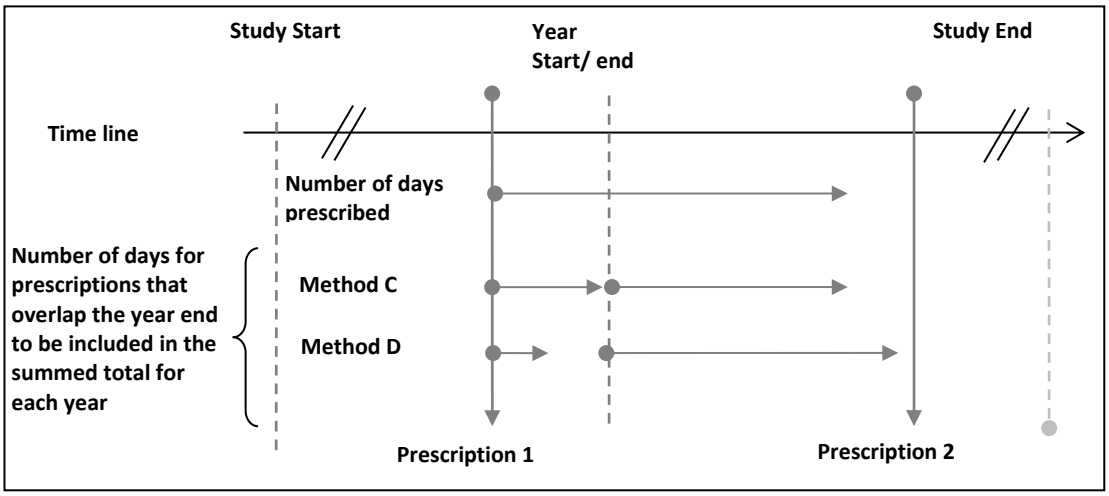
4.4.1.2 Prescription days over the start or end of a year

At the start or the end of a given calendar year, some prescriptions towards the end of the year, could contain prescribed doses that were not intended to be taken during that year (Figure 4-5).

In method C, excess days were passed to next interval. The number of days prescribed after subtracting the number of days to the end of the interval was directly passed over to the following interval to be included in the sum of the days prescribed for the following year.

In method D, the number of days prescribed were shared proportionally between the intervals created by taking the number of days until the next prescription, and dividing this using the year end date to create the two separate time intervals.

Figure 4-5. Two alternative methods to calculate the proportion of days prescribed when the prescription cuts across the interval start or end



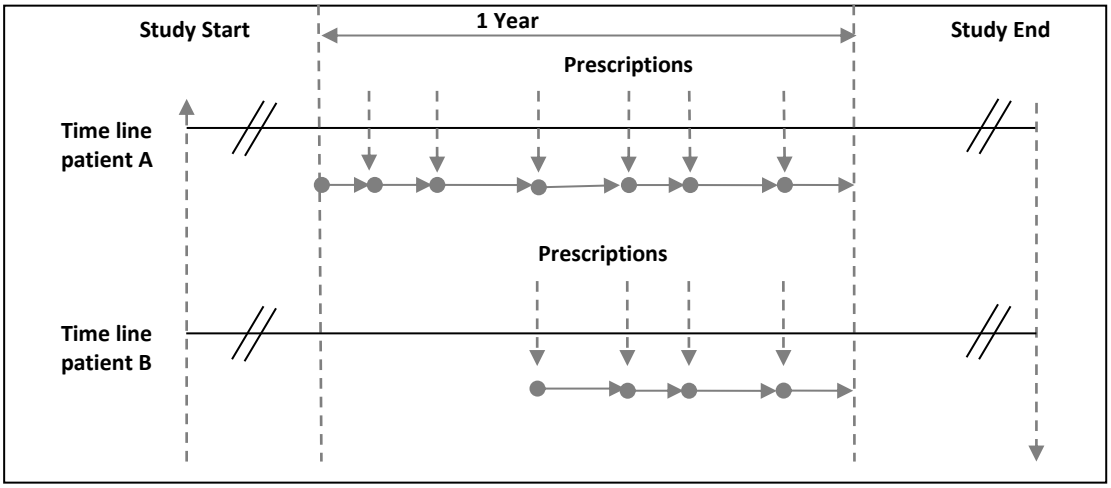
4.4.2 Deriving the denominator PPR calculation

The denominator for the PPR calculation can be either the number of days summed between prescriptions over the year (method E), or the number of days specified for the interval, 365.25 days (method F).

In method E, the number of 'days between prescriptions' were summed to create a total number of days for the prescription intervals within the year interval. The number of days between prescription records were calculated by subtracting the date that the prescription was issued, from the date when the following prescription was recorded or after the number of days prescribed had ended if no further prescriptions were recorded. At the end of the interval, the interval end date was used in place of the following prescription date. At the start of the year, the 1st January in the year was used to replace of the previous prescription date. If the patient was included in the study for the entire duration of the interval (patient A, Figure 4-6), the sum of the days between prescriptions will equal the duration of

the time interval. Adding up days between prescriptions in the intervals accounts for part years (where a patient may enter or leave the data) (patient B, Figure 4-6).

Figure 4-6. Calculating the time interval between prescriptions



If the calculated sum of all of the intervals in the year was less than 7 days, the PPR was not included for that patient year since less than 7 days of ICS use within a year would not indicate that the intention was for the patient to receive a long-term ICS. Alternatively, in method F, the interval duration for the year interval was specified as 365.25 days.

4.4.3 Measuring the PPR using five alternative strategies

Alternative methods to derive the numerator and denominator of the PPR were then combined in four alternative strategies to calculate the PPR, (Table 4-5). The PPR calculated using each individual strategy and summarised using descriptive statistics, including the number of patient years that the PPR was able to be calculated for, the mean, median, mode and the proportion of patient years above 100% and below 50% were presented, and the frequency distribution were presented graphically.

Table 4-5. Five alternative strategies for calculating the PPR

Strategy number	overlapping	excess days	Denominator
1	Method A	Method C	Method E
2	Method B	Method C	Method E
3	Method A	Method D	Method E
4	Method A	Method C	Method F
5	Strategy 1, but results over 100% PPR were censored at 100% PPR		

The first strategy included overlapping days, passing excess days to the next interval, and adjustments to the beginning and end intervals, represented the base case. In the second strategy overlapping doses between prescriptions were excluded, and in the third strategy excess days were shared between years. In the fourth strategy a fixed denominator of 365 days was used, and in the final strategy (number 5) the results were censored at 100%.

In strategy 1, 3 or 4, the number of days prescribed could be greater than the number of days in the interval, since prescriptions may be issued before the previous doses had been used, or more prescriptions given to the patient than required by their recorded numerical daily dose. This would mean that the PPR could exceed 100%. For example a PPR of 500% would represent the patient being prescribed five times the number of doses that were intended to be taken. To address this, an alternative methodology was used to censor the number of days covered by the prescriptions at the value of the number of days in the interval, i.e. any computed value of PPR that exceeded 100% was reset to 100%. The results for censoring at 100% for the base case scenario (strategy 1) were presented as strategy 5.

4.5 Results of data management

There were 6,095,956 ICS prescriptions for the 1,181,033 patient years (292,738 patients), eligible for the analysis. The number of days prescribed (*'numdays')* variable had 97% of data missing required for the calculation of the PPR (Table 4-1). The results of the data management steps to complete the number of days prescribed using the number of doses prescribed and the numerical daily dose are described below.

4.5.1 Number of doses prescribed

The imputation approaches for the missing number of doses prescribed by each prescription, were compared including the results of the remaining number of missing values and the summary statistics for the number of doses prescribed by each prescription (Table 4-6).

Table 4-6. Comparison of the approaches to impute the missing values for the number of doses prescribed

Method	A	B
Approach	Use only the raw quantity x packsize values to calculate number of doses	Use the rules to derive the number of doses prescribed
Records	6095956	6095956
Remaining missing (%)	28968 (0.5%)	433 (0.007%)
Mean	144.1	202.7
Standard Deviation	973.1	107.75
min	1	30
max	720000	3600
median	120	200
Inter quartile range	198	80

Compared with method A, by including the imputation steps in method B, the missing number of doses prescribed and the maximum value recorded were greatly decreased, and many low values were increased. The increase in mean and median results and reduced inter-quartile and standard deviation, indicated that the

imputation approaches for missing values reduce the variation in the 'number of doses prescribed' variable and increased the mean values for the 'pack size' variable, this may have been caused by correcting the records that incorrectly recorded the number of packs in this variable.

4.5.2 Numerical daily dose

Imputation approaches for the missing NDD in each prescription were compared including the results for the remaining number of missing values and the summary of the '*NDD'* value (Table 4.7*).*

Table 4-7. Comparison of the approaches to impute the missing values for NDD

Method	A	B	C
Description	Use only the NDD values recorded	Imputation for NDD based on past and future prescriptions	Imputation for NDD based on past and future prescriptions and NDD based on dosage form
Records	5133751	5447644	6095956
Remaining missing (%)	15.8	10.6	0
Mean	3.5	3.5	3.4
Standard Deviation	2.4	1.2	1.2
min	0.4	0.4	0.4
max	1000	22	22
median	4	4	4
Inter quartile range	2	2	2

The initial imputation method (B) removed the very large '*NDD'* values from the data and reduces the number of missing results from 15.79% to 10.64%. However it made no difference to the interquartile range, mean or median, but reduced the standard deviation as expected. The second imputation method (C) (Appendix 15) reduced the proportion of missing values to zero, but the mean and median, maximum and inter quartile range values remained consistent.

4.5.3 Number of days prescribed

Summary results for the seven approaches to calculate the 'number of days prescribed (Table 4-8. Comparison of the seven approaches to calculate the number of days prescribed showed that for the three strategies where the raw quantity and pack size were used to calculate the number of doses prescribed (Doses prescribed A), the range of the number of days prescribed by each prescription was very wide, with many extremely unrealistic or unlikely values.

The mean number of days prescribed were also lower (strategy 2, 3 and 4) than when the doses prescribed were used to correct and impute the doses prescribed missing values (strategy 5, 6 and 7). Many individual results were also recorded as being very high when doses prescribed A was used. Once these values were corrected using the Doses prescribed (B) method, the extremely high and low results were reduced in magnitude and frequency and the mean number of days across the cohort was increased.

In the four strategies where the rules were used to correct the '*NDD*' (NDD(B) and NDD(C)), the effect of the imputation method of the '*NDD*' appeared to make little difference to the number of days prescribed results, but increased the number of prescriptions where the number of days prescribed could be calculated. The 50th and 90th percentile fall on very similar levels to the number of days prescribed in methods 2 to 7.

Strategy	1	2	3	4	5	6	7
Number of doses	Number of days	Doses prescribed (A)	Doses prescribed (A)	Doses prescribed (A)	Doses prescribed (B)	Doses prescribed (B)	Doses prescribed (B)
NDD	n/a	NDD(A)	NDD(B)	NDD(C)	NDD(A)	NDD(B)	NDD(C)
Prescriptions	154157	5068585	5375438	6008279	5083942	5394979	6036627
Mean number of days	31	47.13	46.82	46.27	62.75	63.02	63.28
Standard deviation	13.87	390.67	380.03	362.85	38.3	38.67	38.05
Median	28	50	48	50	50	50	50
Min	1	0.16	0.17	0.16	0.12	5	5
Max	286	300000	300000	300000	2200	2200	2200
10% percentile	28	0.25	0.25	0.25	30	30	30
25% percentile	28	1.5	1	1	30	30	30
50% percentile	28	50	48	50	50	50	50
75% percentile	30	60	60	60	100	100	100
90% percentile	56	100	100	100	100	100	100

Table 4-8. Comparison of the seven approaches to calculate the number of days prescribed

4.6 Results of the prescription possession ratio

For all of the five strategies (section 4.4.3) used to calculate PPR, a PPR could not be calculated for every patient year included in the cohort. This was due to the years when a patient had less than 2 ICS prescriptions within the year, or when the patient had less than 7 days of intervals included in the data in a year.

For the base-case (strategy 1), there were 28.2% of patient-years with PPR that exceeded 100% (indicating over prescribing), while 32.0% of patient-years had PPR values lower than 50%. By design, strategies 2 and 5 had a maximum possible PPR value of 100%, methods 1, 3 and 4 had a much higher maximum PPR caused by a few very high results, illustrated in the reasonably consistent 90th percentile results for the 3 methods (Table 4-9).

Table 4-9. Comparison of the five strategies to calculate the prescription posession ratio

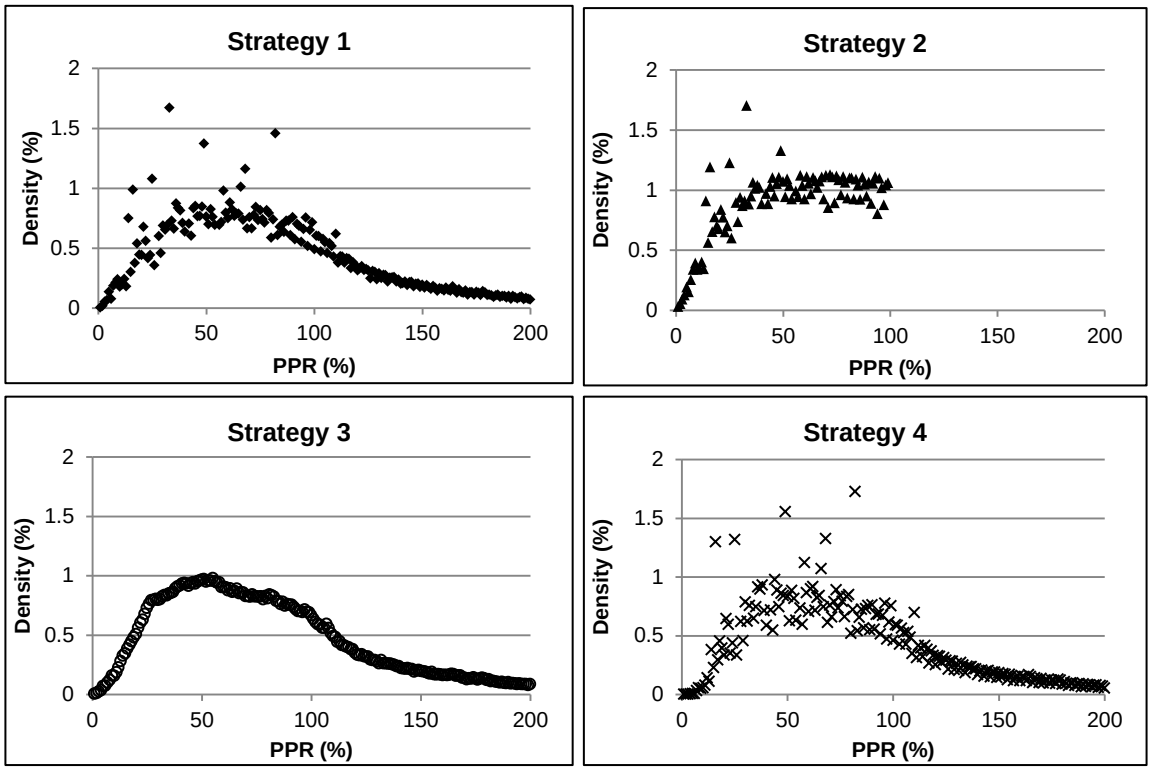
Strategy	1	2	3	4	5
Description	A, C, E	B, C, E	A, D, E	A, C, F	Censored at 100%
Patient years (total=824943)	822503	822503	780767	822526	822503
	99.7%	99.7%	94.6%	99.7%	99.7%
PPR mean	85.5	59.0	92.0	80.2	67.6
St. Dev	71.5	27.0	74.8	58.3	28.9
Min	0.5	0.3	0.9	0.8	0.5
Max	6135.7	100	6821.7	1362.7	100
10% percentile	27.3	22.3	29.5	27.4	27.3
25% percentile	41.6	36.4	47.1	41.1	41.6
50% percentile	69.9	58.6	75.8	66.3	69.9
75% percentile	106.0	82.7	112.8	100.3	100
90% percentile	158.7	97.5	168.9	147.4	100
Number of patient years					
Below 20% PPR	44075 (5.4%)	67108 (8.2%)	29552 (3.8%)	30503 (3.7%)	44075 (5.4%)
below 50% PPR	263545 (32.0%)	330245 (40.2%)	215878 (27.7%)	278355 (33.8%)	263545 (32.0%)
Above 80% PPR	347404 (42.2%)	227740 (27.7%)	364498 (46.7%)	320904 (39.0%)	347404 (42.2%)
Above 100% PPR	232247 (28.2%)	none	250760 (32.1%)	206396 (25.1%)	none

Note: A: Including overlapping days; B: excluding overlapping day; C; pass excess days to next interval; D: share excess days proportionally between intervals; E: interval adjusted for missing data. F: interval set as 365 days.

The proportions of patient-years below 20% PPR and the minimum calculated PPR were approximately consistent across all five strategies. The wide range of PPR values calculated by these strategies was also seen in the large standard deviation presented.

The mean PPR measured by each method for the included cohort years was lower for the strategies where censoring at 100% was imposed (strategy 2 and 5), and higher at around 80 to 90% for the other methods. The frequency density function of PPR by the measurement strategy used is presented in Figure 4-7. The profiles observed are reasonably consistent across the strategies except for strategy 2 where the PPR was censored at 100%.

Figure 4-7. Frequency and distribution of the PPR for each strategy



4.7 Discussion

This chapter described the process for developing the PPR, a proxy measure for adherence to ICS in asthma patients. Data management steps were needed due to missing data in the CPRD in the variables required to calculate the PPR. Alternative approaches to determine the PPR per year were then explored, to determine their influence on the resultant PPR and to be confident in their validity.

Since the selected PPR measure is not a direct measure of patient adherence, the strengths and limitations of the measure must be considered, especially about how well a PPR represents actual adherence and how the measure can successfully be used for analysis.

4.7.1 Impact of data management approaches

The 'number of days' prescribed in the data was often missing, found to be more often recorded when patients were prescribed lower quantities of medicine or had infrequent prescriptions, this may have been when patients were trialling ICS treatment or for shorter term conditions such as other reactive airway diseases. Therefore we would not expect this small proportion of the cohort with the 'number of days' recorded by the prescriber to be representative, and methods were needed to impute the missing data.

The imputation methods used increased the mean number of doses prescribed across the patients, but they also significantly reduced the standard deviation. It is believed that the use of these steps to impute and correct values in the data more accurately modelled actual adherence than the method using the raw data for these variables.

4.7.1.1 Imputing the number of doses prescribed

A number of assumptions were made when choosing approaches to impute and correct the quantity and pack size variables recorded for each prescription before they were multiplied together to give the total number of doses prescribed by each prescription.

When the number of doses prescribed was recorded as 1, this was considered to be more likely to be the number of units prescribed. The BNF was used to complete these values based on the number of doses in the product, however, where multiple pack sizes were available, the largest size was chosen. This ensured that any bias in the number of doses prescribed would cause an over rather than under

estimate of adherence. Only a small proportion of the values were affected and for many of these values the pack size selected would have been appropriate, therefore the effect of these inaccuracies on the calculated 'number of days' variable are likely to be very small.

When the *'quantity'* was greater than 14, it was considered to be unlikely to represent the number of inhalers prescribed, so was replaced with a value of 1. If the intention was to genuinely prescribe more than 14 inhalers, adherence may be underestimated. However, this is considered to be an uncommon practice.

The methods of imputation used for the 'number of days' prescribed, which allowed the PPR to be estimated for more patient years, was based on logical assumptions to correct data.

4.7.1.2 Approaches for completing the NDD

The first approach to impute the missing and outlying NDD values used the other variables available for each prescription with missing data. The second method used the closest completed NDD record in previous and future prescriptions for the same patient with a matching product code within a 2 year period. If the dosage was changed by the prescriber, we would be expect it to have been recorded, and if no daily dose was recorded previously, a future recorded dose was expected to be a reasonable indicator of the intended dose. Only approximately 5% of the NDD results were imputed using this method; therefore, the effect of any errors caused by the imputation would be expected to be low.

The final method, to complete the remaining 10% of the missing NDD results, was based upon the mode for the NDD across the cohort, sub grouped by dosage forms. The majority of the '*NDD*'s for the ICS prescriptions in the cohort for each dosage form were recorded as 2 for DPI and 4 for MDI (Appendix 15). As expected using these rules appeared to make little difference to the cohort mean or median NDD since the new values were based on the population average, but the method reduced the standard deviation and the maximum values recorded. This method would be expected to be the least accurate for specific patients, but was only applied to 10% of the prescriptions.

The imputation of the '*NDD*' appeared to make very little difference to the resulting 'number of days' prescribed, but was useful to complete the '*NDD*' variable making more patient prescriptions available for the analysis. Therefore, the '*NDD*' imputation methods should also be used for further calculations alongside the method using the rules to calculate the number of doses prescribed.

4.7.2 PPR method choice

All of the methods used to derive the numerator and denominator of the PPR calculation generated a similar frequency profile for PPR. The effect of each method choice is discussed below.

4.7.2.1 Overlapping ICS prescriptions

As expected, the inclusion or exclusion of overlapping days in the total of days prescribed per year did not affect the number of years when the PPR could be calculated but had a large effect on the mean PPR of ICS in each calendar year for the study (85.45% vs. 58.97% respectively).

By including the days where prescriptions overlap in the summed number of doses prescribed, adherence may be overestimated. There are a number of reasons why patients may have overlapping prescriptions which could affect the choice of whether to sum the overlaps. For example, patients are likely to receive a new prescription, before their supply from a previous prescription had been completely used to ensure that they have medicine continually available. By summing the overlaps in prescriptions, it was assumed that inhalers would be used sequentially without discarding remaining doses when a new inhaler is prescribed. However, if the ICS prescribed for a patient was changed, the intention may have been to discontinue use of the original prescription and to start using the new one immediately and to discard any leftover doses, making the method that excludes the overlapping days preferable. These intentions are not recorded in the available data, and for the majority of prescriptions, the same product is prescribed, where the expected intention would be to finish the previous prescribed medicine first. Therefore these overlapping doses were included in the sum of the days prescribed over the year.

4.7.2.2 Managing extra doses at the end of a year

By comparing the two strategies used to manage the doses that remained at the end of each calendar year, the first method (to fill the number of days to the interval end and pass any excess doses into the following year) resulted in fewer patient years included and a slightly lower mean annual PPR than the alternative method (to share doses proportionally between the interval before and after the year-end).

This may be explained by the rule used to exclude any year with a total of less than 7 days of prescribing. The excess doses method may have led to fewer days of prescribed medicine being passed to the following year, leading to fewer years with over 7 days of medicine prescribed.

The method where excess doses were passed onto the following year most closely represents a patient taking the medicine as prescribed and then stopping. The alternative method where doses were shared proportionally between the intervals represents non adherence by a patient taking their ICS only intermittently in response to symptoms or under dosed daily throughout the period. We cannot characterise the non-adherence in the available data, therefore, the method of using the medicine as recommended by the guidelines and therefore expected to be recommended by the prescriber is the most appropriate i.e. strategy 1 where excess doses were passed onto the following year.

4.7.2.3 Defining the number of days in the time period for the PPR calculation (denominator)

By comparing the two methods to calculate the denominator; where the days between prescriptions were summed or where 365.25 days was used, was unable to take into account gaps at the start or end of a patients ICS treatment. Therefore, in if the patient enters or leaves the study period part way through a year PPR could be underestimated if 365 days was used. The effect is exacerbated since patients were generally prescribed a larger quantity of medicine in the last year when they were included in the study data.

When the fixed denominator was used, any records from part years could not be included in the study, since part years would have a lowering effect of part years on the mean PPR. Discarding this data would mean that some valuable data at the start and end of a patient's asthma treatment would be lost.

Since the effect of the denominator appeared to have only a small effect on the mean and distribution of the PPR for the cohort, the PPR will be calculated using the sum of the prescription intervals to avoid the lowering effect of patient part years in the data and to allow more years to be included.

4.7.2.4 Censoring at 100%

There was a high degree of variation in the minimum and maximum PPRs identified by different strategies that indicates both under-prescribing and over-prescribing issues of ICS, where over 25% of the PPR exceeded 100% and, 32.0% of years had a PPR of under 50%.

Clinical reasons for over prescribing may include the absence of understanding by the prescriber (or the patient) about what has been prescribed previously, by patients receiving but not filling prescriptions, patients 'stock piling' medicines, patients having inhalers in multiple locations (some which may not be used), patients losing medicines, or simultaneous prescribing of more than 1 ICS drug.

When patients are issued with a prescription for an ICS, they may choose to either not fill the prescription or not take the dispensed medicines. However in good 'patient centred' care where the management of an illness is shared between patient and the prescriber; adherence is likely to be improved. [174] However, if this

excess availability of medicines to a patient leads to improved outcomes, maybe because they always have their medicine available, this could actually represent a cost saving to the NHS which may be interesting to investigate further in a separate study. However this over prescribing could present as a risk to patients if they take over their prescribed dose of medicine.

The two alternative approaches used were to censor the total number of days of ICS prescribed in the year period at 100%, or to exclude from the annual sum of any days of prescribed ICS remaining for each prescription when a new prescription was recorded. In both of these strategies PPR could not exceed 100%. The method using a 100% cut off at the end of the year gave a slightly higher mean PPR (67.56%) than the overlapping supply method (58.97%). Differences in the results are likely to be due to where the prescriptions all overlap (more days prescribed would be lost from the calculation when the method excluding overlapping days were used), or where there was a gap in prescribing, especially at the start of the year in addition to the overlapping prescriptions in a year. The overlapping supply method is not the most appropriate choice for measuring asthma treatment, as it simulates a patient discarding their remaining ICS doses when a new ICS was prescribed, which is unlikely for ICS. Instead the method to censor calculated PPR values at 100% was selected.

In addition to the high frequency of PPR results over 100% prior to censoring, there were also some extremely high outlying PPR results derived from strategy 1. To understand the cause of these anomalous results, records of a small sample of these patient were reviewed and the results (two examples are presented in

Appendix 18). The results showed that the outliers were caused by either patients who frequently received prescriptions with a large number of days prescribed (e.g. patient received monthly prescriptions issued ICS for 200 days), or there was a large amount of 'prescribed days' passed on to the next year and resulted in a high PPR in the following year.

4.7.3 The strengths and limitations of the PPR measure

A variety of approaches were used to test how the results varied when generated using the different definitions. Rational judgements were made when considering the clinical implications of different approaches to consistently model PPR to represent maximum amount of medicine that a patient accessed to.

These methods to define PPR and the data management approaches ensured that the PPR was an accurate measure of the proportion of days that were covered by prescribed medicine per year. However, there are some limitations that need consideration when interpreting the results of the PPR in terms of actual patient adherence. These limitations may influence internal validity (how well the PPR measure is defined within this study) and then the external validity (how well PPR represents adherence).

4.7.4 Internal validity

4.7.4.1 Measuring against a routine daily dose requirement

The PPR calculation used the recorded routine daily dose that was prescribed as recommended by the BTS sign guidelines,[3] however, surveys in the US found that only half of clinicians reported following the guideline to prescribe daily ICS. [175 176] If the intention of the prescriber was not to supply the patient with a daily dose, then

a lower PPR measured would represent prescribing that is not consistent with the BTS/ SIGN guidelines and would also be expected to jeopardise that patients' outcome.

However, this prescribing may be appropriate if the patient's treatment plan was appropriately tailored to their specific needs. For example, patients may be advised in their action plan to step up their ICS or use the ICS when the feel that their asthma is worsening, or in anticipation of being exposed to a known trigger. Some evidence exists to suggest that there may be a benefit to patients from a use-as-needed ICS treatment plan. [177]

4.7.4.2 Adherence could be too low to calculate

PPR can only be calculated for calendar years when the patient received at least 2 ICS prescriptions or if the quantity of doses could not be calculated for more than 2 prescriptions in a given year. In addition, if a patient had less than 7 days of prescribing in an interval the PPR was not calculated. Therefore, there are some patient calendar years where PPR could not be estimated meaning that the PPR could be overestimate since these lowest values could not be calculated.

4.7.4.3 Duplicate records

Prescribing records that appeared to be duplicated were excluded from the PPR calculation, since they were believed to be caused by a simple duplication error. There may be legitimate reasons, such as the patient misplacing their prescription, or remembering that they will be away so need more medicines prescribed meaning that adherence may be underestimated on these occasions, but the effect of this is expected to be small.

It may be more likely that prescriptions on the same day for similar products may be more significant, since a previously written prescription may have been rewritten to correct or to change the medicine or dose prescribed. In this case, the first prescription should ideally be excluded from the calculation; however these specific prescriptions would be extremely difficult to identify and would not be expected to occur frequently in the data. Therefore, the one prescription excluded from the calculation would only have a small effect on the overall PPR calculated for that patient and when considered over the cohort, and the effect would be negligible.

4.7.5 External validity

The main strength of using a PPR to measure adherence is that it allows primary care data in the UK to be used to study adherence; an extremely large cohort, over a long period of time and in a routine clinical setting. This allowed investigations that may otherwise be difficult, prohibitively expensive or impractical to be performed however, there are many potential limitations due to the use of retrospective prescribing data to measure adherence.

4.7.5.1 Medicine taking is not measured

PPR does not directly measure medicine taking, and we must consider that the patient may have been prescribed the medicine, but may not take the medicine as directed. This could be caused by the patient not filling the prescription, by actuating the inhaler and not taking the dose (including poor inhaler technique), by losing their medicines or prescription or by using the medicines out of order so that units reach their expiry date. This could cause the measured PPR to overestimate actual adherence and must be considered when interpreting PPR.

In addition, the amount of medicine prescribed to a patient may be influenced by other factors such as how often the patient visits the prescriber, influenced by their health status, or their personality. Therefore patients with the poorest health, including some patients who may have the poorest actual adherence (if measured by actual medicine taking) may visit the prescriber more often and receive more prescriptions but would have a high PPR.

4.7.5.2 Non adherence is not characterised

The PPR measure cannot characterise the type of non-adherence, i.e. if an individual has a low level of adherence, no differentiation can be made whether they under dose daily or have intermittent dosing maybe as a response to symptoms. Or, a patient could have a PPR of 100%, despite only having a few days with medicine coverage over the first half of the year, but may have overlapping prescriptions over the second half of the year. However, PPR gives the proportion of time covered by the prescribed medicine, which is a useful measure despite the limitations.

4.7.5.3 Medicines from other sources are not included in the data

Medicines could be accessed by patients from other sources that would not be included in the PPR calculation. This could include if a patient has a family member who is prescribed the same medicine, perhaps on a prescription charge exemption, or if the medicines are accessed through an alternative source e.g. whilst travelling and not recorded in the database, or whilst in hospital. The effect of these sources of medicine are expected to only make a small difference to annually measured PPR, but could make a bigger difference for patients with comorbidities who may

spend more time in hospital. But generally, adherence should not be greater than the measured PPR, since patients would not generally be expected to access medicines from other sources, so prescription records represent the maximum availability of medicine to the patient.

4.7.5.4 Combine use of different types of ICS

Some patients may be prescribed more than 1 ICS product to take simultaneously; in the calculation, the days prescribed by each product will be added together, which would over estimate PPR in these cases. This effect would be expected to be minimal, since simultaneous prescribing does not occur frequently in the data and the BTS/Sign guidelines do not recommend this practice. [3]

4.8 Conclusion

The methodology for data management and the alternative approaches to calculate the PPR using the CPRD data in this chapter was able to compare the effect of each of the approaches on the resulting PPR to enable a measure that was as reliable and robust as possible to be developed. The approaches selected in the evaluation of the different methods were to include overlapping days between prescriptions, pass excess days to the next interval (at the year-end), and gaps in the number of days prescribed in the denominator were considered. Once the PPR was calculated, it was censoring at 100%.

The precision of the method to indicate adherence changes is believed to be good since patients who have access to different amounts of medicine have a PPR to reflect this. But, the PPR should be used with caution to determine actual levels of adherence since actual medicine consumed cannot be measured.

Since PPR is not a direct measure of adherence, it is difficult to define the exact relationship between the PPR measured and actual adherence. PPR can however, be considered as a measure of the maximum amount of medicine that a patient has access to (the 'best case'), where the patient's actual adherence to a daily prescribed ICS should not be greater than the PPR. The relationship between the PPR measured and 'real' adherence, measured using a direct method, must be considered when interpreting any results.

By measuring the amount of medicine that a patient has been prescribed, it combines the effect of the patient not attending an appointment where a prescription may be given, or not requesting a new prescription and the effect of the prescriber not choosing to prescribe the medicine. The latter may be for several reasons including the medicine not being appropriate or if the patient expresses that they do not wish to or are unable to take the medicine. Therefore the PPR must be considered to be an estimation, or a proxy for actual patient adherence and care should be taken when using the term 'adherence', including the appropriateness of the regime that they are being measured against.

Despite its limitations, PPR is a useful way to represent adherence in these asthma patients. This method for calculating PPR could be also be applied to other chronic conditions; however the method chosen must be tailored to the specific clinical setting and disease-medicine characteristics, where regular prescriptions are required by the patient.

An example of where a PPR measure is especially useful is for signalling, or measuring adherence changes over time or between subgroups of patients, since this does not rely on exact values, but instead on changes in its value.

The PPR calculated in this chapter was used for the analysis in Chapters 6 to 9, where PPR was used as a proxy measure to represent adherence to monitor the variation of adherence annually and between subgroups of patients. The patient and clinical characteristics that effect this variation over time were explored including a patient's asthma control, which will be described and derived in the next Chapter 5.

Chapter 5 Development of measures for asthma control and severity of asthma

5.1 Introduction

To understand the importance of adherence in asthma and the effect of outcome on adherence, it is important to develop a measure to represent asthma outcome. However, unlike many conditions, a measurable clinical outcome is not clear.

The goal of asthma management, recommended within the BTS/ SIGN guidelines, [3] is to reach complete control of the disease. There are many possible measures that are used clinically to understand a patient's asthma control. These measures can be reported by patient reported outcome, physician reported outcome or clinical tests (Table 5-1).

Table 5-1. The indicators of complete asthma control

Indicator of asthma control	Routinely recorded in CPRD clinical data
No daytime symptoms	No
No night-time awakening due to asthma	No
No need for rescue medication	Yes
No exacerbations	Yes
No limitations on activity including exercise	No
Normal lung function (in practical terms a FEV1 and/or PEF of greater than 80% of predicted or best)	Yes, some data available but may be biased

Some indicators of asthma control are not well recorded in the CPRD data or may be biased or inconsistent, caused by the source of the information or the recording of the information when retrospective records. The choice of what is recorded in the data is the responsibility of the clinician, the quality of these records will therefore vary between patients. The information that is recorded in the data is primarily to record a patient's treatment, but incentives such as QOF may lead to specific information being more likely to be recorded. In asthma these include an

asthma diagnosis, a patients smoking status and asthma reviews, but does not incentivise the recording of exacerbations of symptoms. [178]

The indicators for daytime and night time symptoms and for limitations to activities are likely to be patient reported outcomes, which are subjective measures and are likely to vary between patients and clinicians. A variable for the lung function test was included in the CPRD, but it could be inconsistently recorded or be biased because lung function is most likely to be tested when a patient presents with symptoms.

The occurrence of an exacerbation of asthma symptoms was sometimes recorded in the CPRD, as a specific record. Where this was not directly recorded by the clinician, it can be derived from the information recorded in CPRD such as prescription records to indicative an exacerbation occurrence, or by using a record for referral to secondary care for an exacerbation of asthma. Less severe exacerbations of asthma are able to be treated within primary care, but more severe exacerbations may require the patient to be admitted to hospital. [3]

A patients need for 'reliever' medicine can also be identified from the CPRD data using SABA prescribing data, which although not a direct measure of medicine taking, high SABA prescribing can be used as an indicator of poor asthma outcome. [179]

A patient's asthma severity is also a useful measure to understand the patient's condition. The 2014 BTS/ SIGN guidelines [56] includes defined treatment steps for

patients to maintain asthma control, these steps can be considered to be a proxy measure for the severity of a patients' asthma.

These measures are all expected to be related, where patients with more severe asthma would be expected to have a poorer outcome than those patients with mild asthma. [180] Pharmacotherapy for patients with poor control of asthma may be increased, and consequently lead to an increase in step and hence measured severity.

To develop appropriate measures using the CPRD data to match the data structure for the other study variables, the values for exacerbation, SABA use and asthma severity by treatment step, for each patient were derived measured repeatedly over each calendar year.

5.2 Aim and objectives

This chapter aimed to define and derive variables from the CPRD data to represent patients' asthma control, and asthma severity and to understand the characteristics of these variables over time.

The objectives include:

- To derive variables to identify asthma control by exacerbation occurrence and SABA prescribing, and to represent asthma severity.
- To explore the basic characteristics of these new variables and their trend over time.
- To explore the relationships between asthma exacerbation, control and severity in each year of the study.

5.3 Methods

5.4 Study design and data source

In this cohort study, information from both primary care (clinical therapy and referral files in the CPRD) and secondary care (HES) data for the study cohort (Chapter 3) were extracted to define each outcome measure using a variety of coding methods (Table 5.2). The data was defined by patient year and compared by either calendar year or patient year i.e. by the number of years from when the patient entered the study data.

Table 5-2. Codes and strategy used to identify outcome variables from the CPRD aand HES

Outcome variable and description	Strategy	Codes and variables used to identify data	CPRD files used
Exacerbation occurrence An exacerbation record at two levels of severity: treated in primary care and treated in secondary care	Identifying exacerbation related medcodes (Appendix 16)	Medcodes including the keywords: asthma and exacerbation asthma and admittance/ admit to hospital, emergency prednisolone, oral steroid	Referral and clinical files in CPRD
	Identifying prednisolone prescriptions for exacerbations (Appendix 7)	Prodcodes with prednisolone as the drug substance and oral in the dosage form variable. Prescriptions were identified using the following criteria: 'quantity' <= 20 and 'strength' =25mg, or 'quantity' <= 112 and 'strength' = 5mg	Therapy file CPRD
	Identifying hospital records with asthma as the primary diagnosis code	ICD-10 disease codes: Predominantly allergic asthma (J45.0), Nonallergic asthma (J45.1), Mixed asthma (J45.8), Asthma, unspecified (J45.9).	Primary diagnosis file in HES
Severity **The treatment step as** defined by the BTS/ Sign guidelines, where step 5 is the most severe	Treatment step defined by drug substances prescribed	Prodcodes with drug substance for : salbutamol, terbutaline, formoterol etc	Therapy
	Treatment step defined by ICS strength prescribed	n/a	Therapy
	Treatment step 5 identified by daily prednisolone prescription	Prednisolone prescriptions	Therapy
Control SABA use per day	SABA prescription records	SABA prescriptions	Therapy

***once the codes were identified using the key words, they were manually checked to remove any irrelevant codes.**

5.4.1 Measuring asthma exacerbation from medical and prescription records

Three strategies were used to identify all occurrences of exacerbation, and they were categorised into two levels of severity; those exacerbations that were treated within primary care alone, and those that were more severe and required secondary care treatment.

5.4.1.1 Identifying asthma exacerbation events from clinical and referral records

The first strategy identified exacerbation events (or a recorded referral to secondary care for the treatment of an asthma exacerbation) by screening the patient records in the *referral* and *clinical* files of the CPRD using the medical codes which were identified using the CPRD look up files (Appendix 16).

The output of this process was a data set with patient identifier, a date, a Read code and two dummy variables to define whether the event was related to primary or secondary care.

5.4.1.2 Identifying prednisolone prescriptions for exacerbation from prescribing records

The second strategy identified prescriptions for an oral corticosteroid, [76] at a dose indicative of treatment for an exacerbation. The oral corticosteroid prednisolone is used to treat asthma exacerbation, but is also used as a regular daily medicine for asthma patients who are not controlled by other medicines, i.e. treated within step 5 of the 2014 asthma guidelines. [56] However, prednisolone may also be prescribed for the treatment of other conditions.

To identify the prednisolone prescriptions which are most likely to be prescribed for treating an acute exacerbation in asthma, three criteria must be satisfied:

- Prednisolone prescriptions that were indicative of treatment for an exacerbation (by strength and number of doses prescribed).
- Less than 10 days covered by an individual prescription or quantities/ strength of product typical of treatment for an exacerbation.
- The sum of the days covered by the prescriptions per year must equal less than 90 days.

The prednisolone prescriptions, were classified as being a treatment for an exacerbation if the dosage and quantity were typical of that recommended to treat exacerbation; 40-50 mg daily for at least five days or until recovery, given as 2 x 25 mg tablets or 8-10 x 5 mg tablets daily, [12] as recommended in the BTS/ SIGN guidance.

For an individual prednisolone prescription to be considered to be most likely to be for the treatment of an exacerbation total number of days prescribed needed to be for 10 days or less, and the total number of days prescribed within a year needed to be below 90 days. 10 days of prescribing was chosen since this covers the recommendation that 'at least 5 days' of prescribing for the treatment of an exacerbation in the 2014 and 2016 asthma guidelines. [3 56] Less than Ninety days per year was chosen in this study because it is above the maximum days that are likely to be prescribed per year for a patient to treat exacerbation alone, but less than the number of days prescribed for a patient who routinely was prescribed daily prednisolone.

Any prednisolone prescription identified as being likely to be for the treatment of an exacerbation, but prescribed over the same calendar year as the patient was

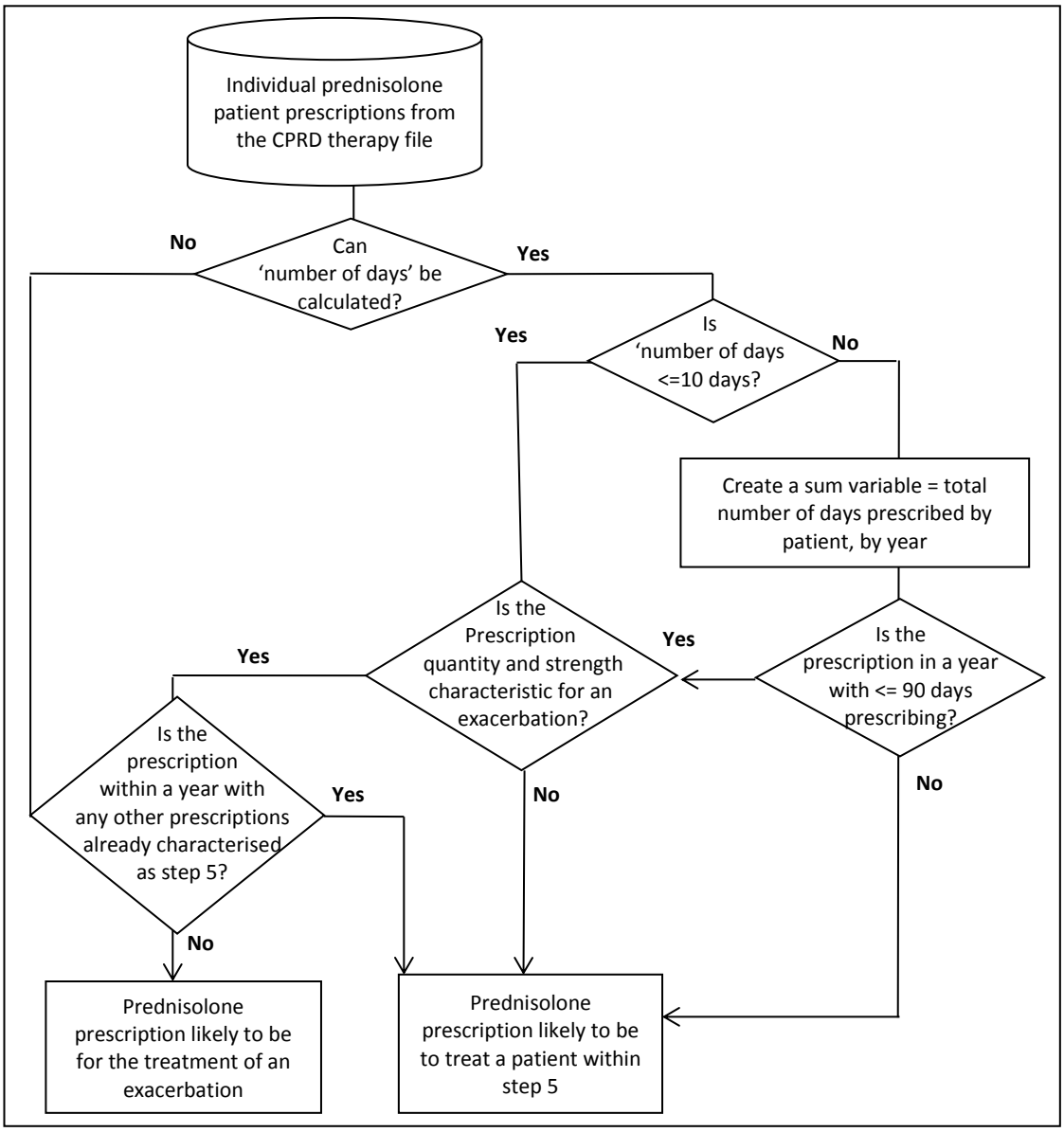
categorised as step 5, and not considered to be prescribed to treat an exacerbation. Since, if a patient was treated within step 5 for part of the year, it is very difficult to prove that any of the other prescriptions were to treat an exacerbation, rather than part of the prescribed daily course for a step 5 patients.

All prednisolone prescriptions issued to the study cohort during the study period were identified and extracted from the 'therapy' files in the CPRD, using the prednisolone prodcodes identified (Appendix 7). The number of days of each prednisolone prescription was measured directly from the number of day's variable (*'numdays'*) or was derived by dividing the '*quantity'* by the '*NDD*'.

A new variable was created to record whether the prescription was related to an exacerbation or step 5 treatment, and a second variable was added to define whether the event was related to primary care (which was a '1' for all of the records identified in this step). These variables were stored for each prescription alongside the patient identifier, a calendar year identifier and a date for the prednisolone prescription.

To complete this new variable, each prescription was assessed to identify whether it was likely to be a treatment for an exacerbation or for a patient treated within step 5 who required a daily prednisolone treatment using the rules in Figure 5-1.

Figure 5-1. Process map to identify a prednisolone prescription for asthma exacerbation or step 5 treatment



5.4.1.3 Asthma exacerbation identified by admission records to secondary care

The third method to identify any asthma exacerbations specifically requiring secondary care was to identify recorded admittances to hospital using linked HES data.

The admittance event related to asthma was identified from the primary diagnosis in the HES data, based on the ICD-10 (10th revision of the International Statistical

Classification of Diseases and Related Health Problems) disease codes [181] (Table 5-2). The process generated a record including the patient identification number, a calendar year identifier, a date for the hospital admission and a dummy variable to define whether the event was related to secondary care, which was recorded as a '1' for all of the records identified by this step.

5.4.1.4 Developing a measure to identify asthma exacerbation

Each of the above methods from both the primary and secondary care data generated a record for each patient with the date for exacerbation and an identifier to indicate whether the exacerbation was treated within primary or secondary care to indicate the severity of exacerbation. Some exacerbations that required secondary care treatment were identified using the primary care data as a referral to secondary care to treat an exacerbation, or by a record from a hospital discharge (in the medical or referral data files).

Using this combined list of exacerbation records, for each patient, any dates occurring within 14 days of each other were joined to create a single event. If a patient had a record for a primary care and a secondary care exacerbation, the primary care exacerbation event was deleted to leave only the secondary care (most severe exacerbation indicator) event record.

Records for exacerbation recorded within a 14 day period are most likely to be multiple records related to a single exacerbation event. This definition has also been used in a previous study. [12]

5.4.2 Measuring asthma control by SABA use

The number of doses of inhaled SABA prescribed (as a proxy measure for the frequency of SABA dosing) was defined as the secondary measure for asthma control in this study. The guideline recommends that patients who use of more than 10-12 doses per day is a marker of poorly controlled asthma. [3] Therefore, in the study patients prescribed with an average of over 10 doses prescribed per day were considered to have poor asthma control.

Prescriptions for inhaled short acting beta agonists (SABA) for the study cohort were identified using 'Product codes' for: salbutamol, terbutaline, and formoterol, and with 'inhalation' recorded as the route of administration (Appendix 7). The numbers of doses prescribed in each prescription were calculated by multiplying the *'number of doses'* in the unit by the number of units prescribed (*'quantity').*

For any missing values, the *'number of doses'* needed to be imputed using the 'packtype' variable, where the product code was used to check the pack size recorded in the BNF. Some data management steps for the *'quantity'* variable were required before it was multiplied with the 'number of doses' variable to ensure the validity of the resulting' number of doses' value imputed:

- If the *'quantity'* was a multiple (up to 8 times) of the 'number of doses', the *'quantity'* was replaced with the multiplication factor to ensure that the quantity represented the number of packs rather than the number of doses.
- If the *'number of doses'* was a multiple of the *'quantity'*, the *'quantity'* was changed to 1 since the number of doses was already calculated, recorded in the *'number of doses'* variable.

- If the *'quantity'* and the *'number of doses'* variable were similar in number, or a multiplication of the number e.g., 100 and 120, or 100 and 360 respectively, which would represent inaccuracies in recording the *'number of doses'* available, the *'quantity'* was replaced by a 1, or by the multiplication factor (quantity/ doses in unit).

For each patient the mean number of SABA doses prescribed per day was calculated for each calendar year for each patient, by summing the number of doses prescribed for each patient over each calendar year, and dividing this by 365.25 days. At each year end and start, the doses were shared proportionally over the 2 intervals created by the end of year, since a SABA is usually prescribed to be used 'as required' so no numerical daily dose is recorded.

5.4.3 Measuring asthma severity by treatment steps

According to the 2014 British guidelines for the treatment of asthma, [56] pharmacotherapy is recommended across each of the five treatment steps, (Chapter 2, Appendix 2), and each step is defined by the classes and doses of medicines that should be prescribed to control patients asthma. Patients treated at the higher steps require increased pharmacotherapy to achieve asthma control. Therefore, the step that a patient was treated within to control their asthma, can be used as a proxy indicator for the severity of asthma. A change in prescribed medication indicates a change in the patient's severity of asthma. For example, a move to a higher step would indicate poor control of symptoms at the current step.

To define the treatment step for an asthma patient based on the 2014 UK asthma guidelines,[56] all asthma related prescriptions for an individual patient were

identified and the classes and dosage/ regimen of medicines were screened by three separate criteria (described in the sections below):

- The classes of medicines prescribed
- Prednisolone prescriptions that are classified as typical of step 5 treatment (daily dose prescribed),
- The ICS dose prescribed

Once a treatment step was defined separately by each of the three methods, the results were combined and the record indicating the highest step that the patient was treated during each calendar year was kept. Any patient without a treatment step assigned to a calendar year when they were included in the study, was investigated and the treatment step added if appropriate, such as when a patient received a LABA but no ICS.

5.4.3.1 Identifying treatment step by prescribed classes of medicines

According to the treatment steps defined by the guideline [56] a matrix was designed to estimate each patient's step per calendar year based on classes of prescribed medicine (Table 5-3). For example, to define a patient as being treated within step 4, the patient must have been prescribed a SABA and an ICS and two of xanthine, leukotriene or LABA and not prescribed IgE agent or magnesium sulphate.

Table 5-3. Matrix to define treatment step by class of asthma related medicine prescribed and ICS dosage

Medicine category	Step 1	Step 2	Step 3	Step 4	Step 5
Short acting beta agonist	✓	✓	✓	✓	✓
Antimuscarinic bronchodilator	?	x	?	?	?
Adrenreceptor Agonist	?	x	?	?	?
Inhaled Corticosteroid	x	Prescribed 1	✓	✓	✓
Chromones	x		?	?	?
Xanthines	x		Prescribed 1	Prescribed 2 *	?
Leukotrienes	x				?
Long acting beta agonist	x	x			?
Anti IgE agents	x	x	x	x	?
Magnesium sulphate	x	x	x	x	?
Prednisolone	?	?	?	?	✓
ICS dose prescribed (mcg/day)	x	200-800	800	2000	2000

Notes: ✓ = must be included, x= must not be included, ?=may or may not be included
Merged cells=one/ two of these must be included,
***patients who are prescribed all three medicines will also be included in step 4.**

Asthma related prescriptions in the *therapy* file were first identified and categorised into the following drug classes (Appendix 1): SABA, antimuscarinic bronchodilators, adrenoceptor agonists, xanthene derivatives, ICS, LABA, mast cell stabilisers (chromones), leukotriene modifiers, anti IgE agents, oral steroids (prednisolone) and magnesium sulphate. Dummy variables were created for each drug class to identify whether they had been prescribed at any time during the year for each patient.

When assigning the treatment step to a patient year prescribed with a LABA inhaler but no ICS (which is not consistent with the guidelines) the LABA was treated as an alternative medicine to an ICS, and these patients were assigned to step 2, or step 3 if additional add on therapies were prescribed. However, for these patient years adherence to ICS was not calculated since no ICS was prescribed, and these years could not be included in any estimation.

5.4.3.2 Identifying treatment step by Step 5 prednisolone prescriptions

Oral prednisolone prescription records were used to categorise patients calendar years as step 5 if they had 1 or more prescription identified as being typical of step 5 treatment within the year.

5.4.3.3 Identifying treatment step by prescribed ICS dose

Doses of ICS prescribed (Table 5-3) were also used to classify patient treatment as step 1, step 2 or 3, or step 4 or 5 based on the BTS/ SIGN guideline. However, it was not possible to differentiate between step 2 and 3 (defined as step 2) and step 4 and 5 (defined as step 4) using this method because the doses prescribe span the two steps, therefore, the lower step was chosen. Choosing the lower step may under estimate the treatment step and therefore the severity of asthma for some patients. However, by combining the estimated step from multiple methods, keeping the highest step identified, if a higher step is confirmed using another method (drug substance or prednisolone prescription, the higher step was used.

5.4.4 Data analysis

Descriptive statistics were used to understand the characteristics of the three clinical outcome measures and then to explore the relationship between those variables. Each clinical outcome variable was presented graphically by calendar year, to observe changes over time that may influence the trend observed in the year since the patient entered the study; which was then presented graphically.

For the occurrence of an exacerbation, the number of patients having experienced at least 1 exacerbation was reported and stratified by the level of severity (whether primary and secondary care was needed). The proportions of patients treated at

each step were also presented to indicate the severity of asthma. The proportion of patients who were prescribed a daily average of over 10 SABA doses prescribed, was reported to indicate the proportion of patients with very poorly controlled asthma.

The relationship between each variable were compared using the Pearson correlation test, and how the relationships changed over the time spent in the study period were then presented graphically by the following subgroups; exacerbation by treatment step and change in treatment step; exacerbation by SABA use and SABA by treatment step.

5.5 Results

5.5.1 Annual prevalence of asthma exacerbation by calendar year and patient year

The proportion of the total number patient years in the study that were recorded as having experienced an exacerbation of either severity was 18% (212301 patients). There were only 5.33% of patient years recorded with more than 1 exacerbation after excluding exacerbations that occurred within a 14 day period of a previous exacerbation.

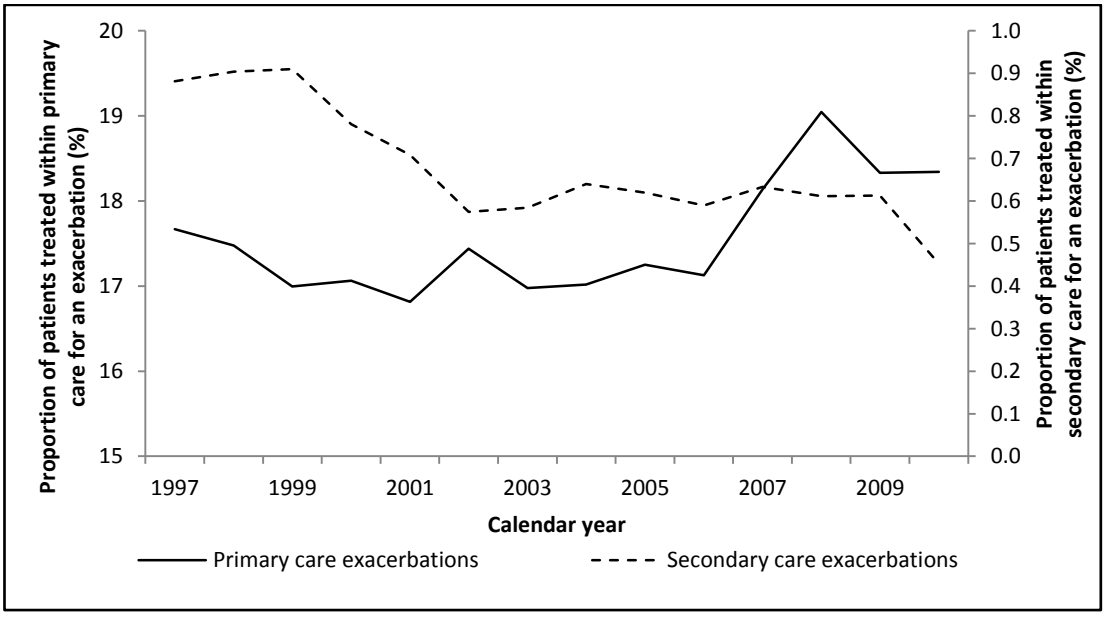
As expected, most exacerbations were only treated within primary care (96.5%) but some required secondary care treatment (3.5%).

In each calendar year, the annual proportion of the total number of cohort patients who had a recorded hospital admission to treat an asthma exacerbation, decreased over time, especially between 1997 and 2002. After 2002 there appears to be a change from a decrease to an increase in the proportion of patients who

experienced a secondary care treated exacerbation in 2002. This may be caused by the delayed impact of the introduction of NHS 'Walk in' centres following their introduction in 2000. [182] An attendance at a walk in centre is recorded within the HES data as secondary care, many of these attendances related to an asthma exacerbation may have been more likely to be previously recorded within primary care. A decrease in primary care exacerbations recorded was also observed in 2002.

The sharp increase observed in the proportion of patients who experienced a primary care exacerbation from 2006 may be as a response to the introduction of the QOF in 2004, where patients may have had more contact with primary care due to the requirement for asthma reviews. [42]

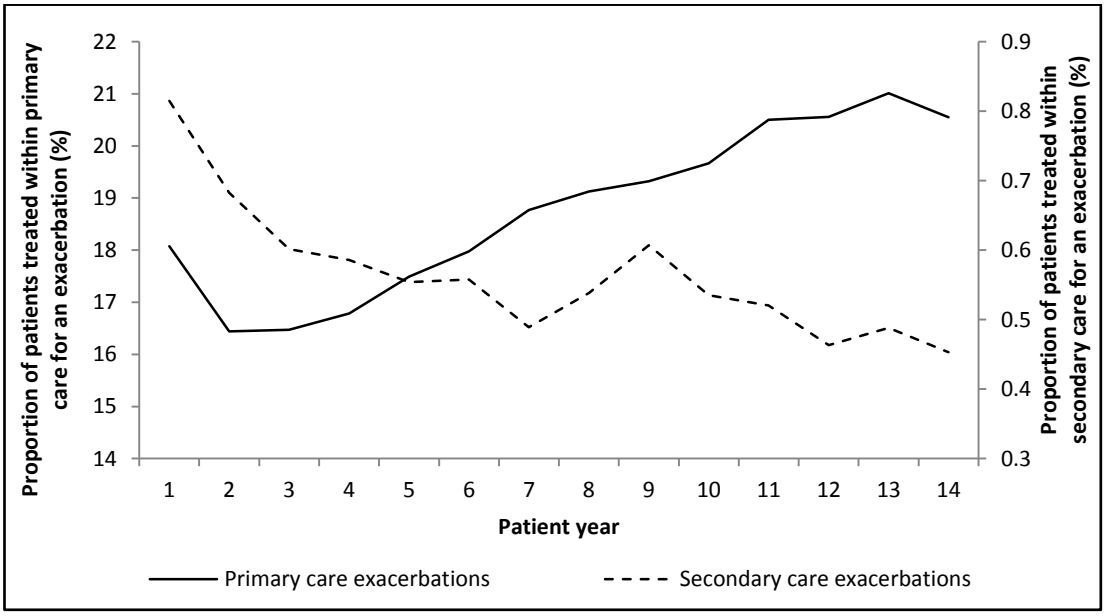
Figure 5-2. Proportion of patients with an exacerbation event in each calendar year



By patient year, the annual proportion of patients who experienced at least one exacerbation treated within primary care, increased by year since entering the study, except for in year 1. The number of patients who had more severe

exacerbations that required hospital treatment generally decreased with increasing time in the study (Figure 5-3).

Figure 5-3. Proportion of patients with an exacerbation event in each patient year



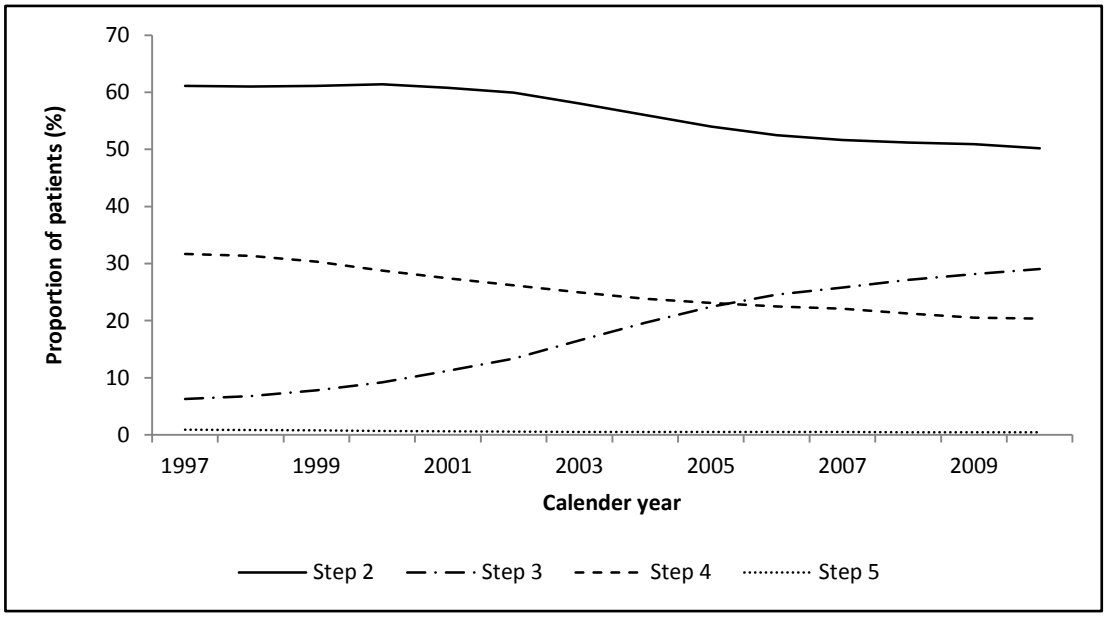
5.5.2 Annual prevalence of patients with different asthma severity by calendar year and patient year

Most of the patients years included in the cohort were recorded as being treated within step 2 (55.38%), with very few patients recorded as being treated within step 5 (0.53%).

From 2001 the annual proportion of patients treated within step 2 decreased over calendar year, after the proportion of patients had remained constant between 1997 and 2001 (Figure 5-4). A similar decrease in the trend was also observed for patients treated within step 4. The proportion of patients treated within step 3 increased over time from 1997 (Figure 5-4), where in 2005 the proportion of patients treated within step 3 exceeded the proportion treated within step 2. This is

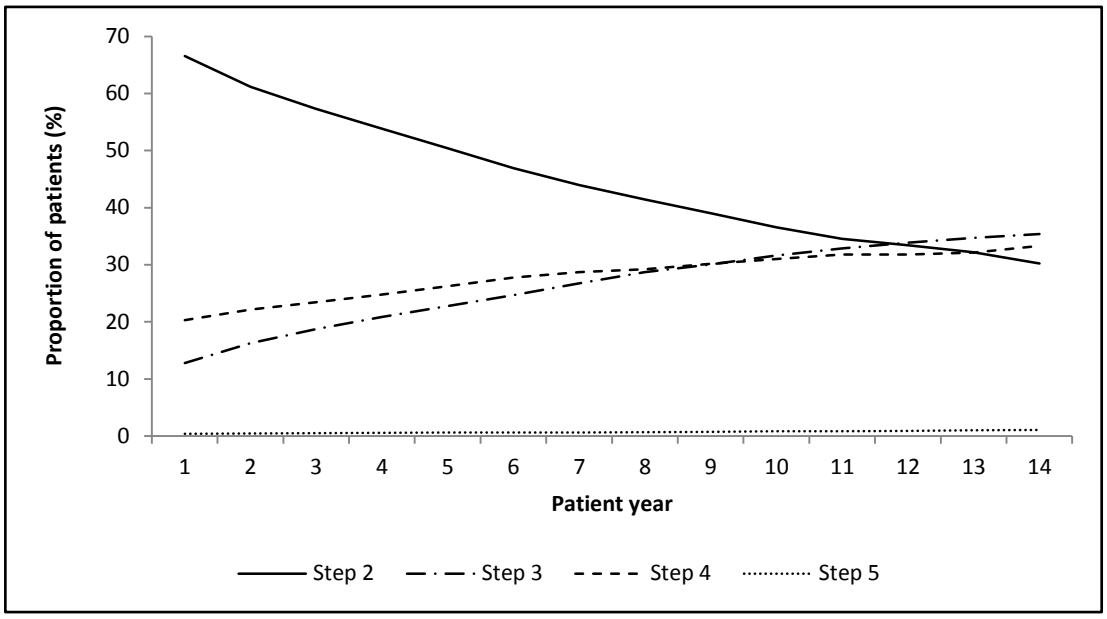
expected to be due to the increased use of LABA following studies that increased confidence in their safety and efficacy in 1997. [183]

Figure 5-4. Annual proportion of patients at the different treatment steps in each calendar year



The annual proportion of patients treated at step 2 decreased by patient year (Figure 5-5). The proportion of patients treated at step 3, 4 and 5 increased by year since entering the study, until the proportion of patients treated within steps 2, 3, and 4 converged after approximately 11 years in the study. This suggests that asthma severity increased throughout the study period (Figure 5-5).

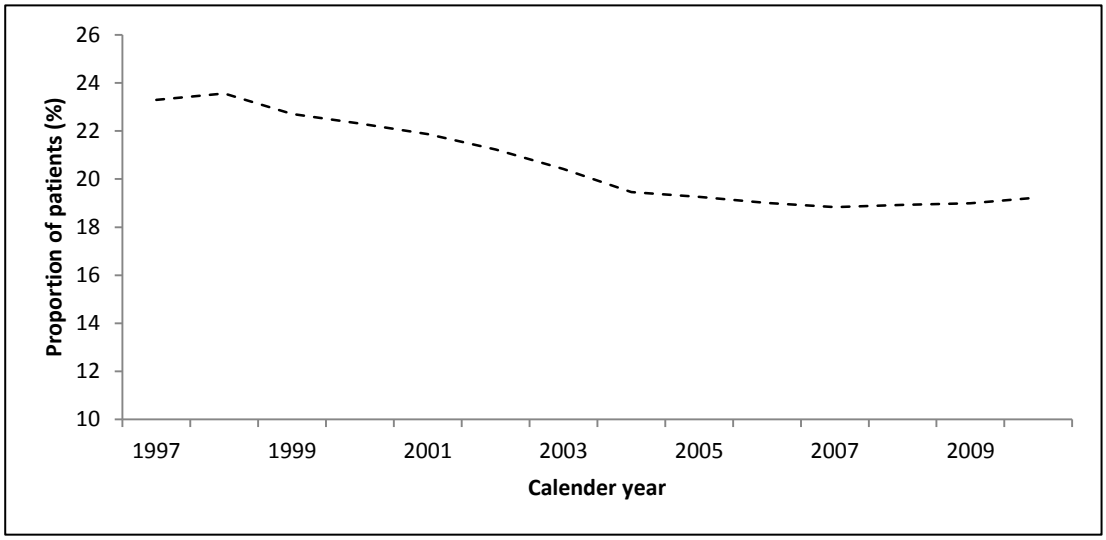
Figure 5-5. Proportion of patients treated within each different treatment step in each patient year



5.5.3 Annual prevalence of patients with poor asthma control defined by SABA use in each calendar year and patient year

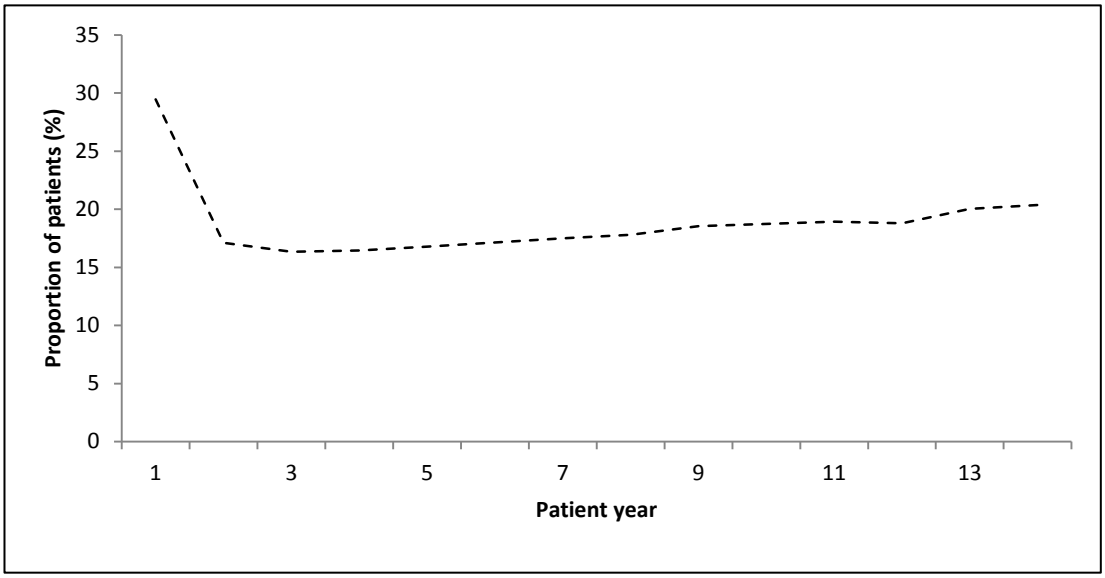
The annual proportion of patients with 'poor control' (using more than 10 doses of SABA) in each calendar year slightly decreased over the time from 24% to 19% (Figure 5-6), except for a slight increase observed at the beginning of the study period between 1997 and 1998. Greater decreases in the SABA use were observed in 1998 and 2004. The decrease in 1997 could be associated with the confidence, and increased prescribing of LABA. [183] The decrease in 2004 could be associated with the introduction of the QOF and the associated asthma reviews which may have improved preventative asthma treatment.

Figure 5-6. Proportion of patients prescribed with SABA use of over 10 doses per day in each calendar year



The proportion of patients who were prescribed an average of 10 or more SABA doses per day increased slightly up to year 14 of follow up after patients entered the study (Figure 5-7) following a decreased in the first year of follow up. This initial high SABA prescribing is likely to be due to patients receiving multiple inhalers to store in different locations.

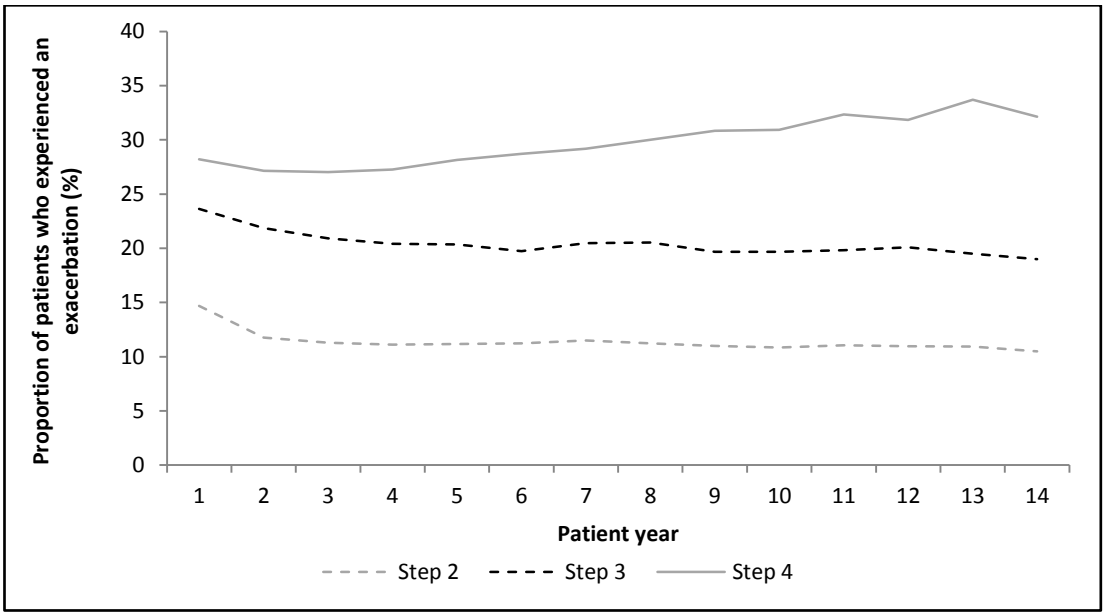
Figure 5-7 Proportion of patients with a mean SABA use of over 10 doses per day in each patient year



5.5.4 Annual prevalence of patients with asthma exacerbations stratified by patients asthma severity

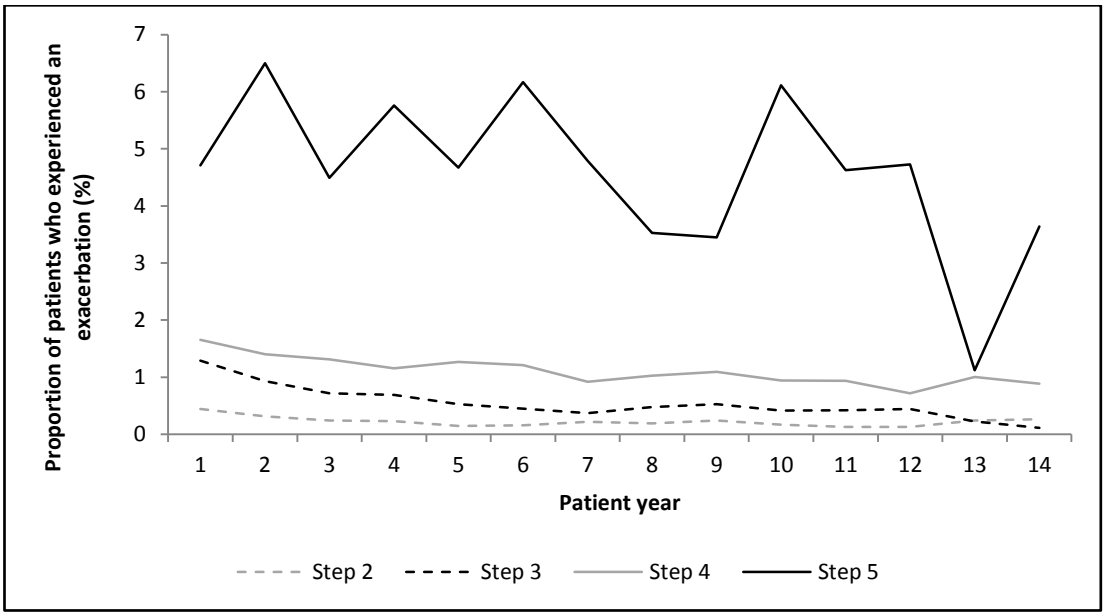
The annual proportion of the study cohort who experienced an asthma exacerbation that was treated within primary care was higher in patients treated within step 4 than those treated within step 2 or 3. The annual proportion of patients who experienced an exacerbation treated within primary care in those treated within step 4 increased over treatment time (Figure 5-8).

Figure 5-8. Proportion of patients with an exacerbation event treated in primary care in each patient year stratified by treatment step



The prevalence of exacerbations in patients treated within step 5 cannot be identified from the primary care records using oral prednisolone prescriptions, because prednisolone prescriptions prescribed to treat an exacerbation to step 5 patients cannot be distinguished from prednisolone prescriptions used as a routine treatment to control asthma in these patients. However, in the results for exacerbations treated within secondary care, a higher proportion of patients treated within step 5 experienced an exacerbation than those patients treated within the lower treatment steps (lower severity of asthma) (Figure 5-9). The drop in the proportion of step 5 patients experiencing an exacerbation at 13 years is likely to be due to variation caused by the low number of patients included (only 1 patient experienced a secondary care exacerbation out of the 89 patients who were treated within step 5 at 13 years).

Figure 5-9. Proportion of patients with an exacerbation event treated in secondary care in each patient year stratified by treatment step



A statistically significant relationship (P=<0.0001) was found between patients' severity of asthma (measured by treatment step) and the occurrence of at least 1 exacerbation, identified from secondary care data within the same year (Table 5-4).

Table 5-4. Correlation between an exacerbation treated within secondary care and the treatment step in each patient year

	Step 2	Step 3	Step 4	Step 5	Total
No exacerbation	652,159 (55.58%)	232,132 (19.78%)	283,110 (24.13%)	5,995 (0.51%)	1,173,396
Exacerbation	1,946(25.48 %)	1,674 (21.92%)	3,698 (48.42%)	319 (4.18%)	7,637
Total	654,105	233,806	286,808	6,314	1,181,033
Pearson chi2(3)=5000					
P<0.0001					

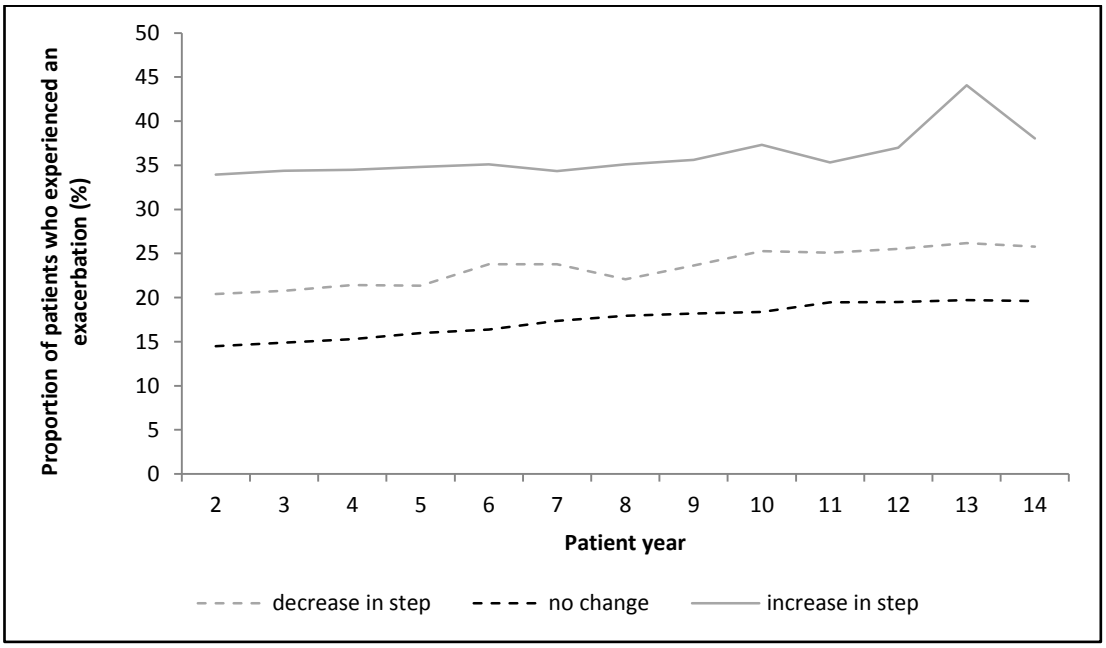
Note: Percentage is the proportion at each step for patient with/ without exacerbation

5.5.5 Trend of asthma exacerbation stratified by change in patients asthma severity

The annual proportion of patients who had experienced an exacerbation over each follow up patient year was stratified by whether patients treatment increased, decreased, or had no change in treatment step in each treatment year (Figure 5-10). As expected, the highest proportion of patients to have an exacerbation (of either

severity) was observed in patients who had their treatment step increased. The lowest proportion (15%) was found in the patients who had no change in their treatment step. In the group who had their step decreased, around 20% of these patients experienced an exacerbation in the same year, but we cannot tell whether the exacerbation occurred before or after the step change. A trend of a slight increase in the proportion of patients experiencing an exacerbation was observed over time, which appeared to be consistent across groups and is consistent with the trend observed in the exacerbation prevalence by patient year (Figure 5-10).

Figure 5-10. Proportion of patients with an exacerbation event treated in primary or secondary care, in each patient year, stratified by changes in treatment step

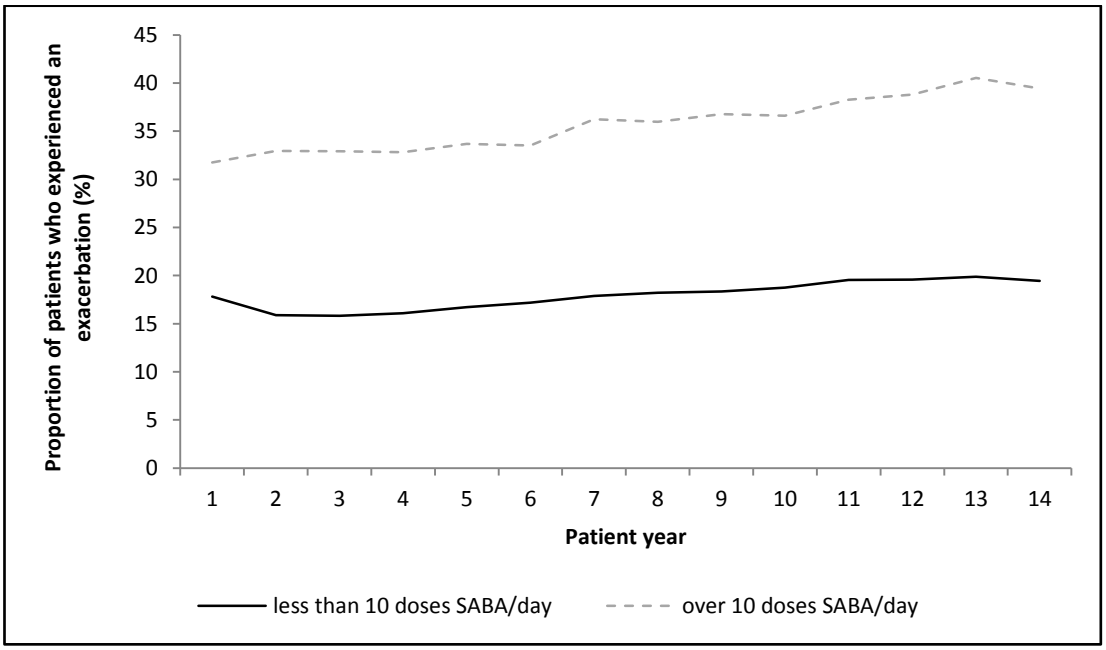


5.5.6 Trend of asthma exacerbation stratified by different levels of asthma control based on prescribed dose of SABA

The proportion of patients who had experienced an exacerbation over each patient year was consistently higher for those patients who were prescribed an average of

over 10 doses of SABA per day (considered to have uncontrolled asthma) than those patients who were prescribed less than 10 doses of SABA per day (Figure 5-11).

Figure 5-11. Proportion of patients with an exacerbation event recorded in either primary or secondary care, in each patient year stratified by SABA use



Overall 18% of the patient years with controlled asthma (based on less than 10 doses of SABA per day) experienced an exacerbation (treated within either primary or secondary care), whereas 35% of the patient years with uncontrolled asthma had an exacerbation recorded. The exacerbations recorded in secondary care, showed that 0.62% of the patients with controlled asthma experienced an exacerbation, whereas 0.69% of the patients with uncontrolled asthma experienced an exacerbation.

There is also significant association (p=<0.0001) between the level of control (based on SABA use) and a patient experiencing an exacerbation within the same follow up patient year, identified by primary and secondary care, and secondary care alone.

Table 5-5. Number of patient years recorded with an exacerbation stratified by levels of asthma control

	Exacerbations in primary and secondary			Exacerbations in secondary care		
	Controlled	Uncontrolled	Total	Controlled	Uncontrolled	Total
No exacerbation	761,351 (79.18%)	200,139 (20.82%)	961,490	928,532 (96.57%)	234,825 (24.42%)	961,490
Exacerbation	173,004 (82.64%)	36,341 (17.36%)	209,345	5,823 (2.78%)	1,655 (0.79%)	209,345
Total	934,355	236,480	1,170,835	934,355	236,480	1,170,835
	Pearson chi2(1)=1300 P<0.0001			Pearson chi2(1)=17.4655 P<0.0001		

Note: Percentage is the proportion at each step for patient with/ without exacerbation

5.5.7 Trend of asthma control stratified by patients asthma severity

A significant correlation was also found between control of asthma (defined by a mean of greater than 10 SABA doses per day) and the severity of asthma (defined by patients treatment step) within the same year (Table 5-6). Patient years identified as step 5 had the highest proportion of uncontrolled asthma, followed by those identified as treatment step 3, step 4 and step 2.

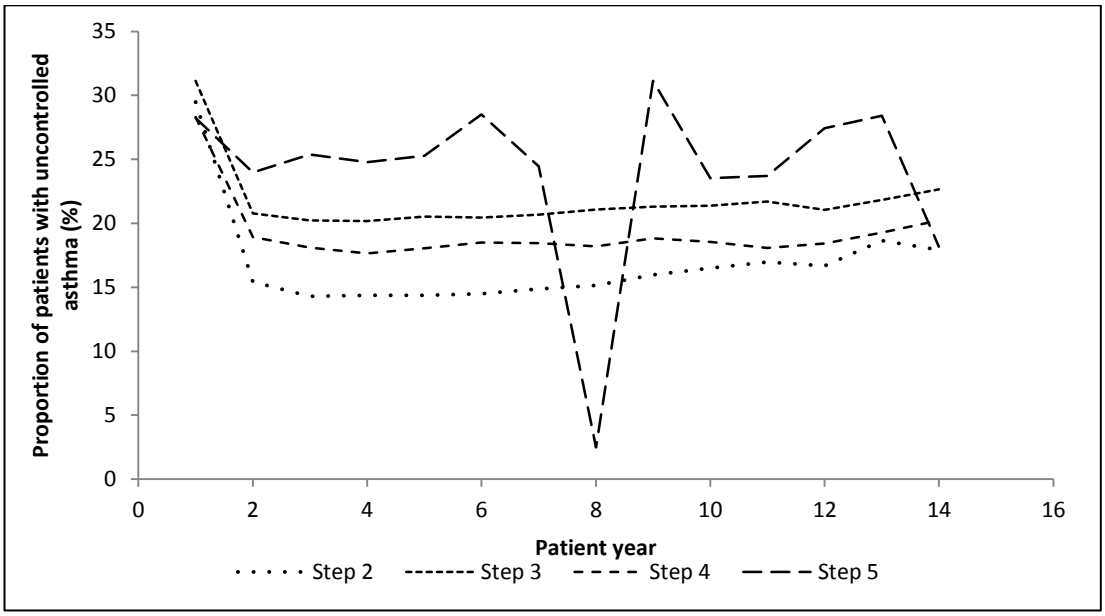
Table 5-6. The number of patient years by asthma status and treatment step

	Step 2	Step 3	Step 4	Step 5	Total
Controlled	524,591 (56.14%)	179,875(19.25%)	225,290 (24.11%)	4,599 (0.46%)	934,355
Uncontrolled	125,228(52.96%)	51,814 (21.91%)	57,837 (24.46%)	1,601 (0.68%)	236,480
Total	649,819	231,689	283,127	6,200	1,170,835
Pearson chi2(3)=1200 P<0.0001					

Note: Percentage is the proportion at each step for patient with/ without exacerbation

Overall, there is generally a slight increase in the proportion of uncontrolled patients at each treatment step over study time (Figure 5-12), except for an unexplained decrease at 8 years for those patients treated within step 5. The overall number of uncontrolled patients treated within step 5 was much lower than the other treatment steps (over the study period a total of 1601 patient years were treated at step 5 out of the total number of uncontrolled patients years in the study of 236480), where the point at 8 years represents only 6 patients.

Figure 5-12. Proportion of patients treated who have uncontrolled asthma, in each patient year, stratified by treatment step



5.6 Discussion

This chapter defined and derived the variables from the CPRD data to represent patients' asthma control using exacerbation records and SABA prescribing, and asthma severity. The trend over time for each of the variables and the relationship between exacerbation occurrence, asthma control, and severity were then explored. The trend over time for each of the variables was then stratified by exacerbation, SABA use or severity. However, the trend over time was generally similar to the trend without the stratification but shifted on the y-axis depending on the effect of the subgroup on the other variable. This is a limitation of this type of analysis, where the effect of the variables on each other cannot be determined when they are both measured over the same year period.

5.6.1 Trend of asthma exacerbation over time

Approximately 18% of the patients experienced an exacerbation each patient year, the majority of exacerbations were recorded within primary care and the majority of these patients did not experience more than 1 exacerbation reported per year.

The proportion of patients treated within secondary care generally decreased over time (calendar year), with the greatest rate of decline seen between 1999 and 2002. This decrease in secondary care treatment may be due to an improvement in the management of exacerbations within primary care or by an improvement in general asthma control within primary care. [6]

By patient year, the proportion of patients experiencing an exacerbation that was managed in primary care generally increased over time. This could be partially explained by the increase observed in primary care exacerbations observed over calendar year; however the increase by patient year is larger. The cause may be due to the patient's asthma becoming more severe and less controlled over time (Figure 5-4) leading to an overall increase in exacerbations, however, an opposite effect was observed in the proportion of patients treated within secondary care. This may suggest that with increasing time since starting treatment, patients visit primary care more often, perhaps because they learn to be more aware of any worsening asthma symptoms, and therefore visit primary care more readily, and prevent secondary care use.

5.6.2 Trend of asthma severity by treatment step over time

The majority of patient years in the study were treated within step 2, with very few patients treated within step 5, especially at the point of entering the study.

By calendar year, the proportion of patients treated within step 2 and 4 decreased, with a corresponding increase in those patients treated within step 3. Step 3 is where patients have further medicine added to the prescribed ICS. This increase in step 3 patients could be associated with the introduction of combination products. For example, Seretide® was launched in the UK in 1999 containing a long acting beta agonist and a corticosteroid (salmeterol and fluticasone) [184] which could cause a shift of patients to step 3.

The longer patients were observed within the study period, the higher the proportion of patients who moved from step 2 to step 3 or 4, suggesting that patients' asthma became more severe over time (progression of disease). However, some patients who were treated at step 2 may have no longer required treatment by ICS for their asthma (decrease in severity), so would have left the study cohort causing the decrease observed in step 2 patients. This could not be tested in this study because only patients' years where they were prescribed ICS were included in the data.

5.6.3 Trend of asthma control by SABA use over time

Approximately 20% of patients each year received an average of over 10 doses of a SABA per day, suggesting that they had extremely uncontrolled asthma. Patients' may have uncontrolled asthma for several reasons, including if the available preventative treatment was not effective maybe because of other disease related factors such as comorbidities or 'brittle' asthma, the patient was not prescribed adequate or appropriate medicines as recommended by the guidelines or if the patient did not adhere to the medicines that had been prescribed. [185] Patients

prescribed preventative medicines also may have received the SABA prescriptions, but they may not have taken the medicine, or have poor technique in taking the medicine. This is a limitation of using prescribing data to represent medicine taking.

On average in the year after entry into the study, the proportion of high SABA use decreased, with approximately 15% fewer patients being prescribed an average of over 10 doses per day. This may have been due to the common practice where patients have many SABA inhalers prescribed initially to store in multiple locations. As patients spent longer in the study, the proportion of patients with over 10 doses per day increased slightly. However, fewer and fewer patients remained in the study as time passed, meaning that the remaining patients were the patients who have had longer term asthma, which may be more severe and less controlled than the patients whose asthma either resolved or they were stepped down to be prescribed a SABA alone.

5.6.4 Relationship between control, severity, and exacerbation occurrence

As expected, patients with more severe asthma (step 4), those patients who had their asthma treatment stepped up and those patients with poor control were most likely to experience a exacerbation treated within primary care.

A slight increase over treatment time in the proportion of patients who experienced an exacerbation, treated within primary care was observed only for those patients treated within step 4. Patients treated at step 4 or 5, who have the most severe asthma, were also the patients who were found to have the poorest asthma control, showing that they are harder to treat and may not respond as well to the available therapies. The patients who had been treated for asthma for the longest

period of time and who had experienced an exacerbation were likely to be the patients who had poor control and consequently were moved up to step 4, especially later in the study, helping to explain the observed trend.

Patients had a much higher chance of having an exacerbation recorded in a year when they were also moved up a treatment step. Since the occurrence of an exacerbation and treatment step change were measured during the same year, we cannot tell which one preceded. An exacerbation may trigger a review of the patient's routine treatment for their asthma [3] and may highlight that the patient was not adequately controlled at their previous treatment step, so would therefore have their treatment increased. A patient's treatment step may also have been increased before the occurrence of an exacerbation if their asthma control was found to be worsening.

Patients, who had decreased their treatment step, were also found to have a slightly higher chance of having an exacerbation in the same calendar year than patients with no step change. This may be caused by the patient's asthma not being adequately controlled at this new step. A patient's treatment step would be decreased if the prescriber considered their asthma to be well controlled. This lack of symptoms has also been reported to be a cause of poor adherence [186] perhaps due to their belief that their condition wasn't as serious. This suggests that changes in routine treatment represent a high risk time in a patient's treatment and consequently should be more closely monitored.

5.6.5 Relationship between control and patient asthma severity

A higher proportion of the patients years, where patients were treated at Step 5 were found to use a mean of over 10 doses of SABA per day, the measure used as a proxy to uncontrolled asthma, whereas step 2 patients had the lowest proportion of years where patients had high SABA use.

The proportion of patients with poor control appears to be higher for patients treated at step 3 than step 4. This is unexpected and is not consistent with the previous findings where these patients were more likely to experience an exacerbation. Which raises a question of why step 3 patients are more likely to have uncontrolled asthma, than those in step 4, but are also less likely to experience an exacerbation than step 4 patients. It may be because step 4 patients have better control of their asthma, because of the additional use of an 'add on' medicine such as a LABA, and/ or are prescribed a higher dose of ICS and therefore have less need to use a SABA to relieve symptoms.

5.6.6 Strengths and limitations of the outcome measures

5.6.6.1 Asthma exacerbation

Three strategies were used to identify the occurrence of an asthma exacerbation, and then combined to try to capture every exacerbation that a patient experienced, classified by two levels of severity, those that required treatment within primary care alone, or those that required secondary care (hospital) treatment. Using this composite measure risks double counting exacerbations, but this was minimised by excluding exacerbations that occurred within 14 days of another because any exacerbation event identified that occurred within 14 days of a previous one was

considered to be related to the same exacerbation. The choice of 14 days was a compromise between underestimating the occurrence of exacerbation by using a longer period, or over estimating exacerbation events using a shorter time period.

The ideal measure would have been a recorded exacerbation event in a read code within the primary care data, however these were found to be frequently missing meaning that the use of this measure alone would underestimate exacerbation. Instead, most primary care exacerbations were identified using prednisolone prescriptions, where data management steps were used to minimise the inclusion of any prednisolone prescriptions prescribed for other conditions. Any patients who were treated with daily prednisolone at step 5 were also excluded. This may have excluded extra patients who were prescribed over 90 days of prednisolone to treat recurrent exacerbations as they would have been misclassified as a patient treated within step 5. However, we would only expect a very small number of patients to be misclassified, and if a patient was treated within step 4 but needed repeated prednisolone prescriptions (over 90 days prescribed), it is likely that classification within step 5 may be more appropriate for these patients.

A limitation of using prednisolone to indicate exacerbations treated within primary care is that we cannot use this measure for any years when a patient was treated within step 5, since it is difficult to reliably differentiate between daily prednisolone prescriptions and those prescriptions indicated to treat an exacerbation.

Limitations in the identification of all primary care exacerbations could be caused by the variability in the severity level where patients are prescribed oral prednisolone, this could be due to choices by the prescriber or the patient. Also, some patients

events where they received a rescue dose of prednisolone may have been lost due to a belief that they were treated within step 5 of the guidelines. This could lead to primary care exacerbations being under reported.

The method to identify the more severe exacerbation events by admission to hospital for asthma was more robust, since it is based on a specific record for when a patient was admitted to hospital for asthma either recorded in the primary or secondary care data. This level of exacerbation, where a patient uses secondary care is also the most important to understand, since it is where the main cost for treatment to the NHS, society and to the individual lies. The main limitation of this method is that it relies on a correct recording of asthma as the primary diagnosis for admission to hospital, or for the discharge letter to be recorded in the primary care data.

Asthma outcomes based on the occurrence of a severe exacerbation are commonly used in asthma studies, when retrospective data are used, either administrative claims or primary or secondary care data. They are often defined as hospitalisation or an emergency department visit [187-190] or also includes a requirement for systemic corticosteroids for at least 3 days. [191] [14]

It is difficult to validate the methods used in this study, due to the available prevalence data including different populations or based on the overall uk population. However, the methods used aimed to identify exacerbations as completely as possible and to avoid under reporting of exacerbations. This is especially important for secondary care exacerbations, where the HES data was

used, since not all exacerbations within secondary care are likely to be fully reported in the primary care data.

5.6.6.2 Asthma severity by treatment step

The variable to represent severity of asthma exacerbation used treatment step as a proxy measure based on the intensity of treatment required to achieve good asthma control. This has been considered to be the most clinically useful measure of asthma severity. [192] However, other studies have used different categories such as the GINA step categories for severity based on forces expiratory volume in 1 second, [193] data which is not available in this study data set. Step was determined using three strategies and combined to try to identify the step as accurately as possible, and to try to maximise the precision of the assignment of the correct step to each patient year.

Where a patient was identified as being treated at two different steps, the higher step was assigned to the patient year. The limitation of this is that the patient may have only been treated at the higher step for a short period within the annual interval. Another over estimation of step could have been caused when patient had not been prescribed all of the medicines at the same time. For example, if a step 3 patient was prescribed a SABA, an ICS and a leukotriene, but this leukotriene was stopped and a LABA started, the patient would appear to be treated within step 4. (due to the prescribing of 2 different classes of medicine from the choice of leukotriene's, LABA's and xanthene's). The number of patients that this over estimation would be expected to impact would be limited, especially since patients were also classified by the ICS dosage prescribed, which would be expected to

correct the majority of these patients who had their step over estimated by the drug class strategy alone.

Not all prescribing is expected to be consistent with the guidelines. Therefore, some patients will not fit into the step criteria used in this study, or may be incorrectly classified e.g. if they were prescribed a LABA without an ICS.

Only one previous study was found to classify asthma severity by treatment step using a similar methodology to this study [194], however many studies, both prospective and retrospective, have defined step, where the methodology was not specified [195-198] or using data for only the drug prescribed. [199]

5.6.6.3 Asthma control by SABA use

SABA prescribing was used as proxy measure of asthma control. This method has been used previously in both prospective and retrospective studies and is used as an indicator for poor control within general practice [3] However many studies used a quantity of SABA [189 200 201] often greater or equal to 3 units per year was used as an indicator [179 190], but use of Use of >2 canisters of SABA per month was also used to indicate that the patient may be at risk of exacerbation. [202] Other studies instead used the ratio of controller to total medication. [201]

Based on the BTS/ Sign guideline recommendations the selected criteria to classify a patient as having poor control, selected for this study (a mean of over 10 doses per day, [3] calculated over each year in the study) would indicate that the patient had extremely poor control, hence will only identify the most uncontrolled patients.

Periodicity of a year may be too long to identify incidents of poor control; however, a measure based on a shorter period may reflect actual use even less accurately since SABA inhalers may be stored prior to or during use. SABAs are used to relieve symptoms, meaning that patients are encouraged to carry their inhaler with them. For this reason patients may be prescribed multiple inhalers to keep in multiple locations or patients may misplace inhalers and therefore some over prescribing of a SABA may be appropriate, which would incorrectly indicate poor control of asthma symptoms. Some of these extra inhalers prescribed SABA may not be used within the inhalers expiry date and therefore remain unused. However, if patients had fewer SABA inhalers prescribed, they may not have a SABA available to them when required so may experience more severe exacerbations and consequently may require more frequent hospital treatment. Another limitation to this method is that some patients pay not be classified as having high SABA use since the level of detection is set very high.

Despite these limitations, the measure of a mean >10 SABA per day, would represent extremely high use, exceeding the effect of any normal prescribing, so can be considered to be a useful measure to identify patients who had very poor control of asthma.

5.7 Conclusion

Despite the complexities and the limitations presented in deriving clinical outcome, severity and control, the clinical outcome variables should provide a reliable indication of the patient's condition. However the precision of these methods to reflect the actual outcomes must be considered when interpreting the results. For

example, a patient's assigned treatment step is not likely to differ greatly to the one measured from the data, and patients actual use of SABA may not be able to be measured, but a patient with very high SABA prescribing is likely to be using more than a patient with lower quantities prescribed.

These types of measures lend themselves to investigations at a population level to identify 'at risk' groups or to define policies to benefit the majority of patients. Any limitations or inaccuracies in the data would be expected to become less significant to any conclusions made in a very large cohort, since we have attempted to make the error in the measured variables as random and unbiased as possible.

From the results presented in this chapter, the expected interactions between each variable were found; where patients with poor control and with more severe asthma have a higher chance of having a poor clinical outcome. One exception to this was for patients treated within step 3, who were at higher risk of exacerbation than those treated at step 4. This understanding both helps to validate the appropriateness of the outcome variables developed, and is useful to aid the interpretation of the analysis results later in the study.

Chapter 6 Factors influencing adherence to ICS in asthma patients over time

6.1 Introduction

To understand which patients would benefit most from adherence interventions, it is important to understand the patient variables and their relationship with adherence to identify which patients, identified by their specific characteristics, are at higher risk of poor adherence. In addition, it is especially important in chronic conditions such as asthma, where treatment may continue over many years, to also study how adherence itself and its relationship with other factors may change over time. This enables points in a patient's treatment to be identified where an adherence intervention would be most effective and efficient at improving adherence and hopefully lead to improved patient outcomes. A variety of patient factors have been reported to influence asthma patients' adherence to ICS in previous literature, however, very little research was found to have evaluated the correlation over time with these variables, where a time has been considered previously, usually only a short duration was included. [140 141]

The trend in adherence by calendar year was investigated to enable changes in adherence at specific dates or years to be observed. Changes by calendar year could be caused by factors such as policy changes, new medicines being introduced to the market or by changes in the guidance available at the time of treatment. Adherence was then compared by patient year, to understand how adherence changes over the progression of a patient's treatment.

Simple statistical tests were used to quantify differences in adherence between patients with different characteristics by subgrouping patients by each characteristic and comparing their adherence. Then the influence that these patient variables had on adherence and how this changed over the progression of a patients' treatment was explored using a graphical representation. Comparing the effect of each patient variable on adherence one by one allowed the mean adherence between patients with different characteristics to be compared and to observe how this effect may change over time.

The analysis in this chapter was also useful to inform the decisions about which variables to include and how they should be included in the more complex regression model in Chapter 8 where the effect of multiple vriables on adherence was studied.

6.2 Aim and objectives

This chapter aimed to explore how adherence to ICS, varied between patients with different characteristics (including clinical outcome). The objectives included:

- To understand the trend of adherence over calendar year and patient year.
- To determine the difference between mean levels of adherence, when sub-grouped by the characteristics of each variable
- To understand the effect of patient variables on adherence and how this changed over the course of patients' treatment.

6.3 Methods

6.3.1 Data source

This cohort study used data derived from the CPRD for each patient in the study cohort (Table 6-1 and Appendix 17) including individual patients' adherence to ICS (measured using a PPR; Chapter 4) asthma control (Chapter 5) and characteristics (Chapter 3). Each variable was derived by calendar year and an additional variable to indicate the number of years that the patient had been followed in the study was also included (the 'patient year'), used to represent the progression of a patient's treatment.

Table 6-1. Patient characterisics for subgroup analysis

Category	Variable
Patient- demographic	Gender
	Age in years
	Region of living
	Marital status
Patient -lifestyle and comorbidities	Comorbidities
	Smoking status
	Pregnancy
Socioeconomic status	Socioeconomic status
	Prescription exemption
Therapy related factors	Adverse effects from ICS/OCS
	Drug substance
Condition related	Exacerbation
	Severity of asthma and change in severity
	Control

6.3.2 Trend in annual mean PPR of ICS

To investigate how adherence to ICS for the cohort changed over time, the mean PPR for patients included in the cohort was measured in each patient year (i.e. by year since the patient entered the study) and by calendar year. The numbers of patients included in the mean calculation for each year were also presented in an over laid chart for comparison. This aided the interpretation of the mean adherence

data, since if fewer patients are included in the mean, greater variance may be expected.

6.3.3 The trend of annual PPR stratified by different patient variables

The mean adherence was calculated for the subgroups for each of the variables (gender, marital status, etc.), by combining the results for each patient year that was included in the cohort. The results are reported in a table for each variable as the mean PPR by variable subgroup, also presented as a difference from the overall mean PPR.

The differences in the mean PPR between subgroups for each variable, were tested statistically (by combining the PPR results from all patient years). Since PPR was censored at 100%, it cannot be considered to be normally distributed; therefore, the non-parametric tests (Appendix 17) were used to compare the groups. The Wilcoxon-Mann Whitney test was used to test the median PPR between two categorical variables; the Spearman rank test was used to test PPR in two ordinal variables, and the Kruskal Wallis test was used to test mean PPR in more than two categorical variables. A value of $p<0.05$ was defined as a statistical difference.

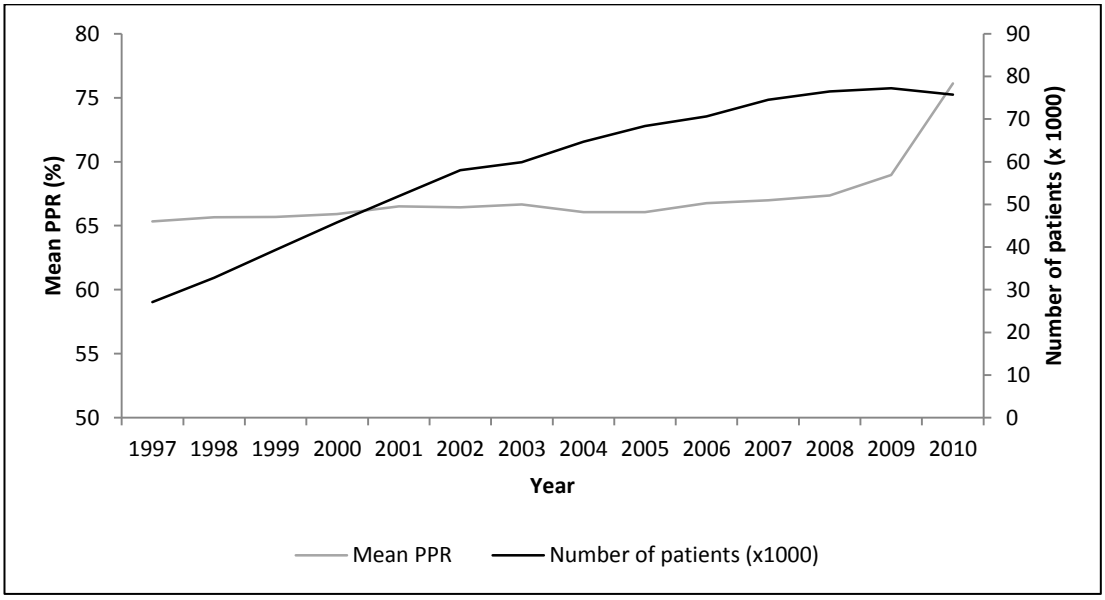
The mean adherence was then calculated for each sub group for the variables previously used, by patient year, and presented graphically using a separate chart to show the effect of each variable including clinical outcome on adherence.

6.4 Results

6.4.1 Trend of annual mean PPR of ICS in asthma patients

The annual mean adherence remained constant until a sharp increase from 2009. 2009 represents the final year where patients were included in the study period, but there are no factors related to the method or any external factors that are the obvious cause for this increase. The number of patients eligible for adherence calculation increased by calendar year (Figure 6-1).

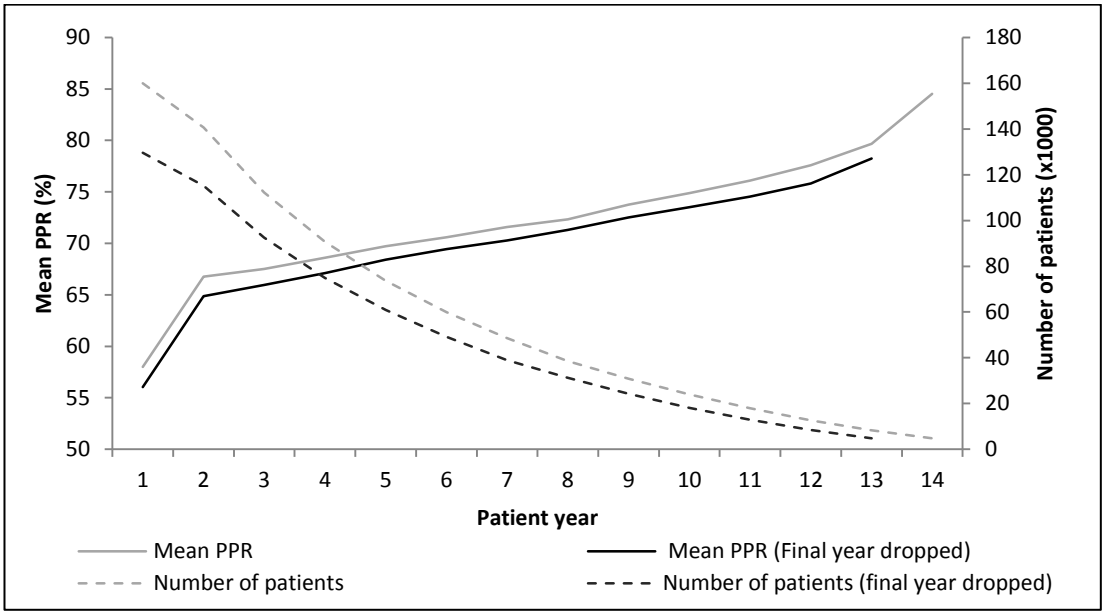
Figure 6-1. Annual number of eligible patients and mean PPR, in each calendar year



The mean PPR in each consecutive follow up patient year increased from around 55% to 85% over the 14 years of patient follow up. A pronounced increase from years 1 to 2 was observed (Figure 6-2). The increase in PPR in year 1 is likely to be caused by those patients who received their first ICS prescription, who may also have increased contact with health professionals which may in turn increase adherence. An increase was also noted at year 13. This increase is most likely to be

attributed to be caused by the lower number of patients in the study at 14 years (4750 patients).

Figure 6-2. Number of patients and mean adherence by PPR, in each consecutive patient year



To investigate whether the difference in year one was caused by the patients with only one year available, the patient's final year of data was excluded from the study data set (this removed any patients with only 1 year of data, but also discards the data when differences could have existed due to the reason for the patient leaving the cohort). Excluding the final year of data for each patient was found to make very little difference to the trend observed, but the mean PPR was slightly lower.

6.4.2 The effect of patient variables on adherence

The annual PPR across all patient years, by each subgroup of patients with different characteristics is presented in Table 6-2.

Table 6-2. Mean PPR per patient year stratified by different patient variables

	Variable name and sub group		Observations (N)	Mean PPR (%)	Difference from mean PPR	P value
	Adherence to ICS		822494	67.56	n/a	
Patient (demographic)	**Gender**	**Males**	356585	68.52	+0.96	<0.0001
		Females	465909	66.82	-0.74	
	Age in years	**12 to 18**	101806	61.52	-6.04	<0.0001
		20-25	52830	61.75	-5.81	
		26-35	129012	64.68	-2.88	
		36-45	174305	66.51	-1.05	
		46-55	174678	69.88	+2.32	
		56-65	189863	73.18	+5.62	
	Marital status	**Single**	53790	65.44	-2.12	0.0001
		Married	110541	68.24	+0.68	
		Widowed	2191	71.96	+4.40	
		Divorced	7214	68.69	+1.13	
		Separated	2536	69.68	+2.12	
		Engaged	130	70.09	+2.53	
		Co-habiting	3441	67.86	+0.30	
		Remarried	864	66.66	-0.90	
		Stable relationship	271	74.0	+6.44	
		Civil Partnership	41	78.44	+10.88	
	Region of living	**North East**	17981	69.0	+1.44	0.0001
		North West	152747	67.69	+0.13	
		Yorkshire	46162	67.40	-0.16	
		East Midlands	33187	66.57	-0.99	
		West Midlands	102659	68.14	+0.58	
		East of England	108303	66.92	-0.64	
		South West	96821	68.74	+1.18	
		South Central	100586	67.65	+0.09	
		London	85516	67.17	-0.39	
		South East	78532	66.44	-1.12	
Patient (lifestyle and comorbidities)	**Comorbidities (Charlson score)**	**score of 2 or 3**	191200	69.62	+2.06	<0.0001
		score of 4-5	26932	71.84	+4.28	
		score of 6-9	6871	72.12	+4.56	
		score of 1-14	716	73.87	+6.31	
		Score of 15-18	7	100	+32.44	
	BMI	**below 18.5**	269	65.82	-1.74	0.0008
		18.5 to 25	2060	65.80	-1.76	
		above 25	4387	68.68	+1.12	
	Pregnancy	**pregnant**	12235	62.19	-5.37	<0.0001
		not pregnant	810259	67.64	+0.08	
	Smoking status	**non smoker**	256440	66.62	-0.94	0.0001
		smoker	246359	70.01	+2.45	
		Ex-smoker	118757	70.63345	+3.07	
		Passive smoker	1340	66.39038	-1.17	
Socioeconomic	**Exempt from prescription charge?**	**Not exempt**	649581	67.12	-0.44	<0.0001
		Exempt	172913	69.19	+1.63	
	Socioeconomic status patient home	**1 (least deprived)**	181094	66.44	-1.12	<0.0001
		2	185371	66.99	-0.57	
		3	161400	67.67	+0.11	
		4	161489	68.38	+0.82	
		5 (most deprived)	128303	68.80	+1.24	
Therapy	**Signs of adverse effects from ICS/OCS**	**oral thrush**	5322	77.95	+10.39	<0.0001
		osteoporosis	2420	71.67	+4.11	<0.0001
		adrenal suppression	2	99.32	+31.76	0.3280
	Drug substance	**beclometasone_y_n,**	514780	68.52	+0.96	<0.0001
		budesonide_y_n,	134409	69.63	+2.07	<0.0001

	Variable name and sub group		Observations (N)	Mean PPR (%)	Difference from mean PPR	P value
		ciclesonide_y_n,	1242	77.27	+9.71	<0.0001
		mometasone_y_n,	1329	67.36	-0.20	0.5911
		fluticasone_y_n,	233164	65.92	-1.64	<0.0001
Condition	**Exacerbation-primary care**	**no exacerbation**	658750	67.19	-0.37	<0.0001
		exacerbation	163744	69.04	+1.48	
	Exacerbation-secondary care	**no exacerbation**	816209	67.56	+0.00	0.1745
		exacerbation	6285	67.02	-0.54	
	Exacerbation-in Previous year primary care	**no exacerbation**	540427	65.42	-2.14	<0.0001
		exacerbation	120624	67.39	-0.17	
	Exacerbation-in previous year secondary care	**no exacerbation**	656831	65.78	-1.78	0.4738
		exacerbation	4220	65.38	-2.18	
	Treatment step	**2**	385009	66.17	-1.39	<0.0001
		3	196806	69.61	+2.05	
		4	235103	67.96	+0.40	
		5	5576	73.50	+5.94	
	Change in treatment step	**Decrease in step**	44243	71.33	+3.77	<0.0001
		No change in step	688012	70.56	+3.00	
		Increase in step	63301	74.16	+6.60	
	SABA use	**Below 10 doses per day**	782470	66.74	-0.82	<0.0001
		Over 10 doses per day	40024	83.53	+15.97	

A lower adherence was recorded for the following patient and demographic factors: Females, younger patients, those who were recorded as being single or cohabiting, followed by those who were married, patients who lived in the East Midlands, East of England and the South East of England. The characteristics associated with the largest decrease in mean adherence were younger age and pregnancy. The characteristics associated with the largest increase in mean adherence were older age, being in a civil partnership or stable relationship, a large number of comorbidities, adverse effects associated with ICS, higher treatment step and an increase in treatment step and high SABA use (representing poor asthma control).

The effect of primary care exacerbation on adherence did not show a large effect in this comparison and the effect of a secondary care exacerbation on adherence was not found to be statistically significant.

6.4.3 Trends of annual mean PPR in asthma patients with different demographic factors

All of the subgroups for the patient demographics had a similar general trend by patient year, where mean PPR increased over time, but the mean PPR between some subgroups were affected slightly differently over treatment time (Figure 6-3).

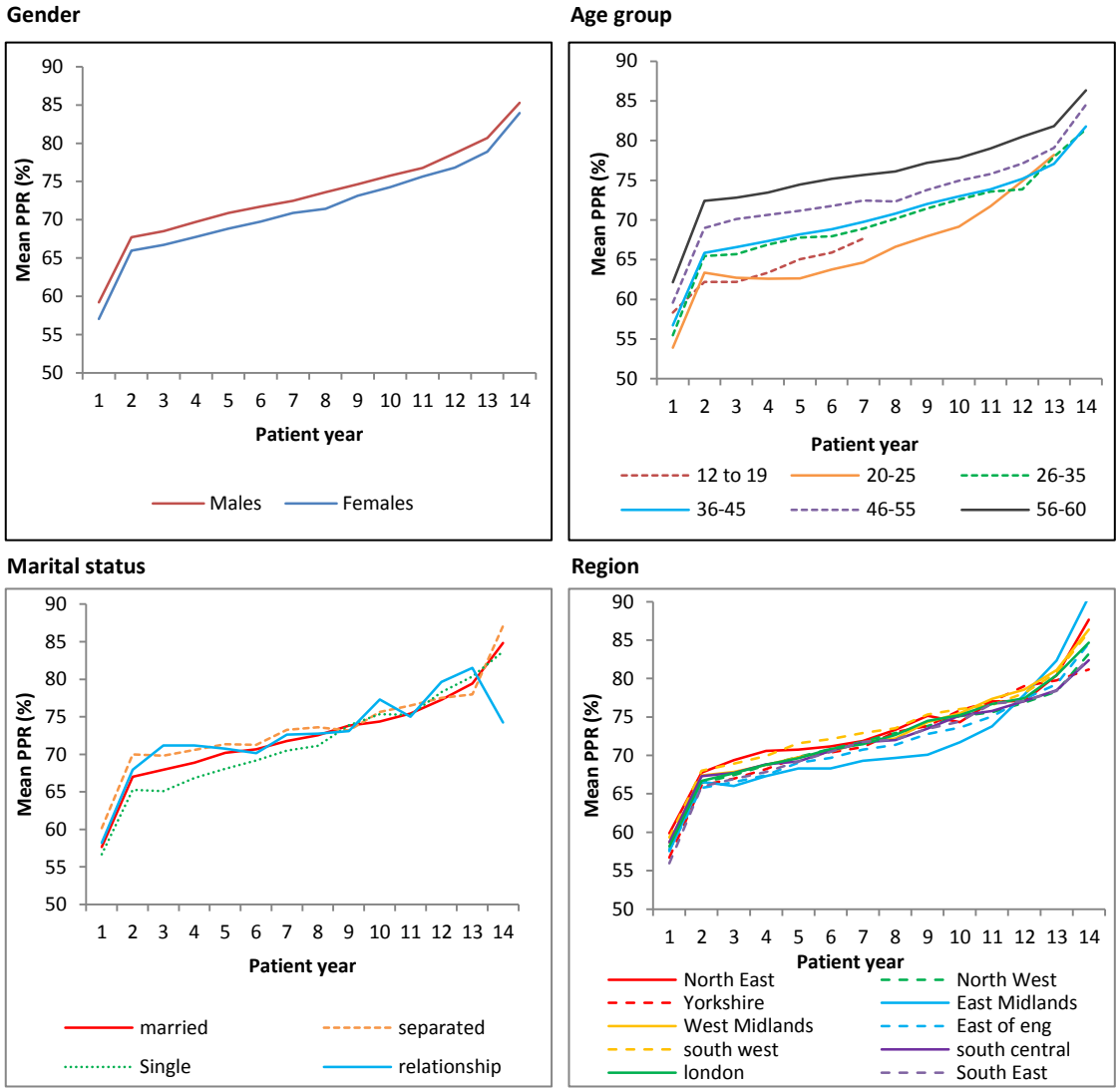
Mean PPR for males was found to be consistently slightly higher than the mean PPR for females.

Mean PPR generally increased with patient age, however, initially the youngest patients (age 12-19 years) had a higher PPR than some of the older age groups (especially 20-25 year olds, who generally had the lowest measured PPR). The data for the youngest age group was available for a maximum of 7 years (patients age 12 to 19).

For marital status, a similar trend was seen to the over time when compared with the sub grouped mean data, however, after the 9^{th} year of treatment, the patients who were single patients no longer had the lowest mean PPR.

By region of living, no clear trends were observed. But adherence increased at the fastest rate over time in the East Midlands.

Figure 6-3. Mean PPR in each patient year, stratified by patient related demographic factors



6.4.4 Trends of annual mean PPR in patients with different lifestyle and comorbidities patient variables

All of the subgroups for the patient lifestyle and comorbidity factors generally had a similar trend by patient year, but the PPR for some subgroups were affected differently over time (Figure 6-4).

By patients smoking status the mean PPR was generally highest for smokers, and was lowest for those patients who were recorded as non-smokers. There was a

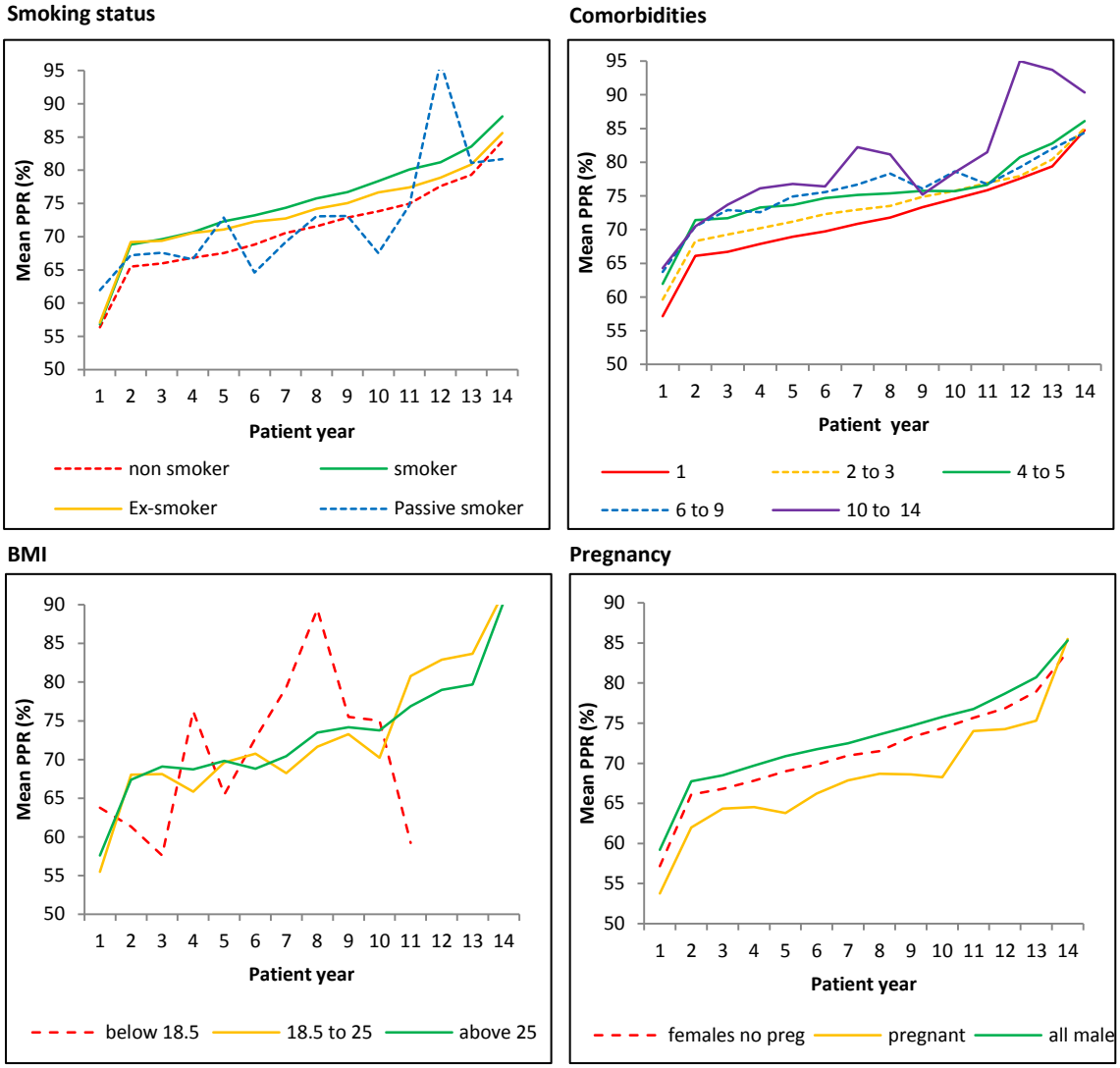
large amount of variance in mean PPR calculated for patients recorded as passive smokers, but a low number of patients were included.

By Charlson comorbidity score recorded at entrance to the study period mean PPR was found to be generally higher with increasing comorbidity score. Very few patients (n=7) had a score of 15-18, but for these patients the PPR was found to be very high. This effect was relatively consistent over time spent in the study compared with the other groups.

BMI was not recorded for many patient years (16% of all years where could be measured). When recorded, patients who had a BMI of over 25 (classified as overweight) generally had a slightly higher mean PPR than for patients who had a BMI recorded within the normal range. By patient year, the relationship between these two categories reversed several times, however, the number of patients included was reasonably low compared with the overweight BMI category especially from 9 years onwards (n=69, decreasing to n=15 at 14 years).

In a year where a patient had a record of being pregnant the mean PPR was slightly lower than for those patients with no pregnancy record, this was seen throughout the study period.

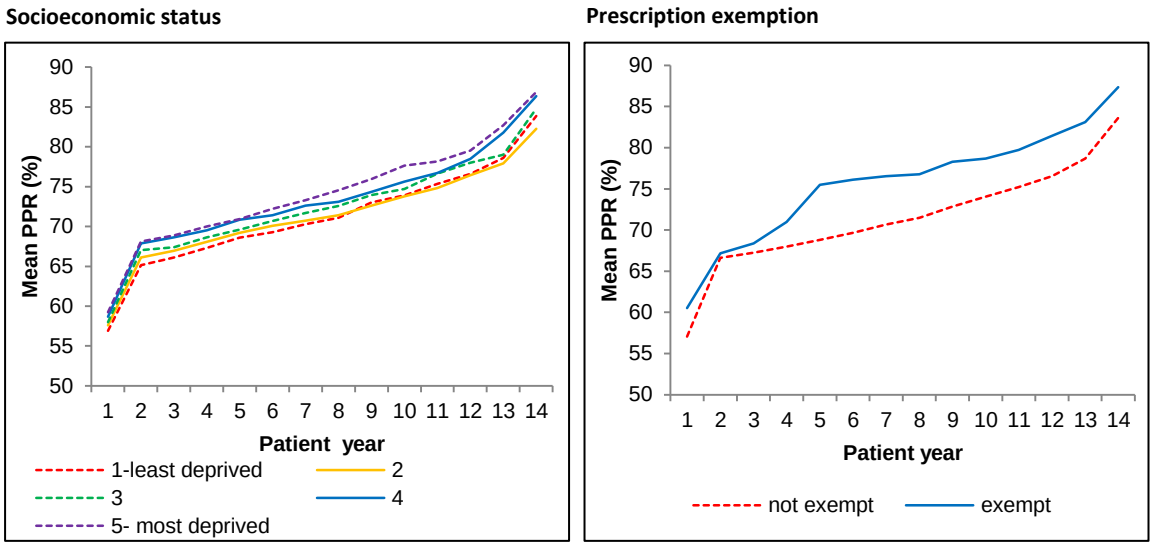
Figure 6-4. Mean PPR in each patient year, stratified by patient lifestyle and comorbidity factors



6.4.5 Trends of annual mean PPR in asthma patients with different socioeconomic status related factors

All of the subgroups for the patient socioeconomic status factors generally had a similar trend by patient year. Where the patients who live in areas with that are classified within the most deprived quintile had the highest mean PPR and patients who were exempt from prescription co-payment had a consistently higher mean PPR over the number of years that they remained in the study than those patients who paid for their prescriptions (Figure 6-5).

Figure 6-5. Mean PPR in each patient year, stratified by socioeconomic status related factors



6.4.6 Trends of annual mean PPR in asthma patients with different therapy related factors

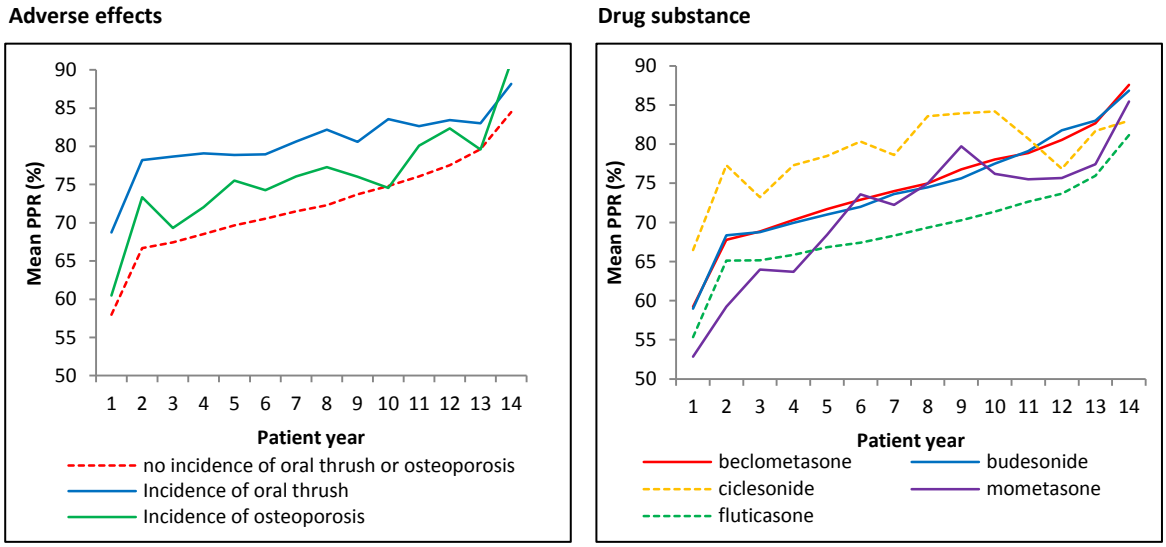
All of the subgroups for the therapy related factors generally had a similar trend by patient year, but the mean PPR for some subgroups were affected differently over time (Figure 6-6).

Patients who had at least one incidence of oral thrush recorded or a record for osteoporosis, had a mean PPR that was higher than those patients who had no record for either condition, where patients with osteoporosis, had consistently higher mean PPR than those for oral thrush. This effect was relatively consistent by patient year, but swapped over at the 13th year of treatment where the number of patients with oral thrush (n=70) and osteoporosis (N=27) had decreased to low numbers.

Throughout treatment, patients taking ciclesonide had the highest recorded PPR, with fluticasone, the lowest. Those patients, prescribed mometasone, had a mean

PPR that increased at the greatest rate throughout the course of treatment. From year 4, the mean PPR for those patients who were prescribed Fluticasone was lower than for all other drug substances.

Figure 6-6. Mean PPR in each patient year, stratified by therapy related factors



6.4.7 Trends of annual mean PPR in patients with condition related variables

All of the subgroups for the condition related factors generally had a similar trend by patient year (Figure 6-7).

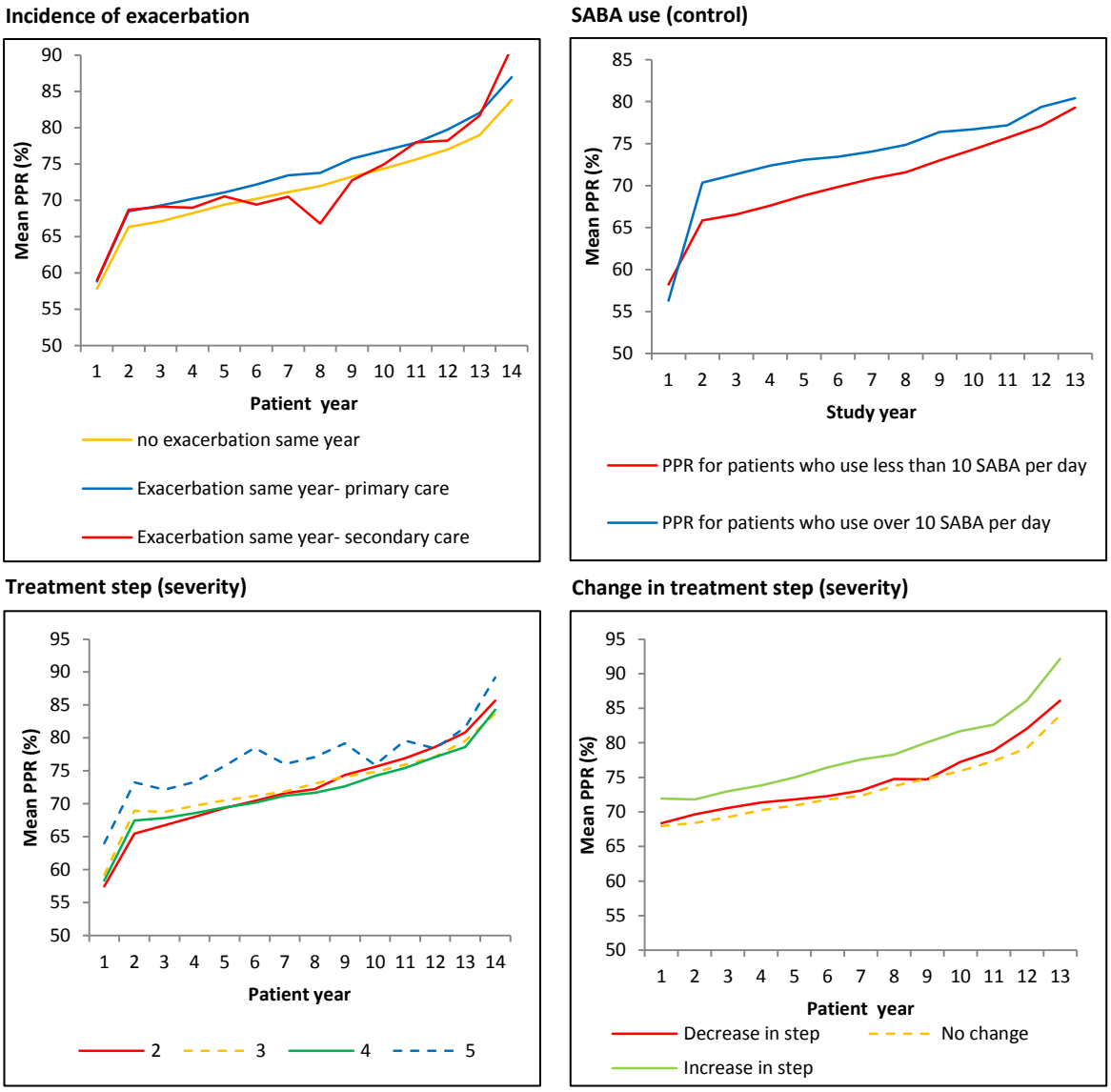
The patients, who experienced at least 1 exacerbation that were treated within primary care, had a consistently higher mean PPR, than those patients that had not experience an exacerbation when measured during the same year. No consistent trend was observed for patients who experienced an exacerbation that required treatment within secondary care.

Patients with high SABA use (those who used an average of over 10 doses of SABA per day over each calendar year), almost consistently had a higher PPR than those patients with low SABA use

When comparing PPR level, by treatment step, the mean PPR for steps 2, 3 and 4 generally were lower than patients who were treated within step 5 each. There was little difference between the trends in mean PPR for all subgroups by patient year.

The mean PPR for those patients who changed step from the previous year, were higher than for those patients who had not changed step, where patients who had increased step had a higher mean PPR than those patients who had decreased step.

Figure 6-7. Mean PPR in each patient year, stratified by condition factors



6.5 Discussion

This chapter investigated how adherence to ICS may vary between patients with different characteristics and treatment time. These are summarised in Table 6-3 and discussed in the following sections.

Table 6-3. Summary of mean PPR results when subgrouped by patient variables

	Variable	Subgroup with lowest PPR	trend over time	Consistent with previous evidence
Time	**Years in study (treatment duration)**	Fewer years in study (especially year 1)	Steeper increases in the first and last years of the study period	No, but the studies were over a shorter time period
Patient	**Gender**	Female	Consistent	No
	Age in years	Younger age	Consistent , but 12-19 years higher than 20-25 at entrance to study	Yes, lowest adherence reported in adolescents
	Marital status	Single or remarried patients	Inconsistent	Little evidence
	Region of living	Living in East Midlands or South East, East of England	Inconsistent , mean PPR in East Midlands increased at faster rate	Little evidence
	Smoking	Non smoker	Consistent (except for passive smoker)	Little evidence
	Comorbidities	Fewer comorbidities	Consistent	Little evidence apart from in depression
	Pregnancy	Pregnant	Consistent	Little evidence
	BMI	Within normal range, not consistent over time in study	Inconsistent	Little evidence
SES	**Socioeconomic status**	Lower deprivation	Consistent (generally)	No
	Prescription exemption	Non exemption	Consistent	Yes
Therapy	**Adverse effects from ICS/OCS**	No adverse effect recorded (adrenal suppression- not significant)	Consistent	Little evidence
	Drug substance	Fluticasone (Mometasone- not significant)	Consistent, but not mometasone (greatest increase)	Little evidence
Condition	**Severity of Asthma**	Lower treatment step (not step 5), then step 4 at 6 years	Consistent (for step 5), other steps less consistent	Yes
	Change in step from previous year	No change, then step decrease	Consistent	No evidence found
	Asthma control (SABA use)	Good control	Consistent	Little evidence
	Primary care exacerbation (same year)	No exacerbation	Consistent	Difficult to compare
	Secondary care exacerbation (same year)	Not statistically significant	Inconsistent but exacerbation lower, between year 5 and 9	Difficult to compare

6.5.1 Trend of annual mean PPR by calendar year and patient year

Mean PPR by calendar year was found to be relatively constant between 1997 and 2006, but increased until the end of the study in 2010. By patient year number an increase in mean PPR was observed throughout the study.

A specific cause for the increase observed after 2006 by calendar year was not found in the literature; however, SMART therapy was first introduced in 2007, where Symbicort® (a combination inhaler of ICS and a LABA) was recommended as a maintenance and reliever therapy. This therapy is associated with the patient taking more doses of ICS. [203 204] The time lag in the uptake of this new regimen on prescribing may have aligned their use in the UK with the increase in ICS prescribing observed in the data, which would translate in the adherence measure used here to be an increase in adherence.

The increase in adherence over time year shows adherence is increased with increased years of treatment for asthma. Few previous studies have considered adherence over a long enough period of time to measure changes in adherence over the course of treatment, but where studies were found that have measured adherence over time although of a lot shorter duration (12 or 24 months), the opposite effect on an individual's adherence, where adherence decreases over time has been found. [140 141]

Other studies that have considered the effect of interventions to improve adherence often have found a short lasting effect before adherence decreases again, [205] which suggests that these interventions may not have a long lasting increasing effect on adherence over time.

The sharp increase in PPR by patient year, recorded between years 1 and 2 may have been caused by a low annual PPR for patients in their first year of treatment. Many factors could cause this low PPR such as patients who were initially prescribed ICS intermittently or for a short duration to control their asthma before it was considered necessary to step up to ICS treatment permanently, or by patients doses being adjusted either at the start of treatment or when they had newly registered with a practice or because of the younger age of the patients at the study start.

A small increase in the mean PPR was also recorded for the patients who had remained in the study for 14 years, however the patient numbers were low so may have more associated variation. For all patients who were included in the study period for 14 years, the 14th year will have coincided with the final year of the study period, 2010, where PPR was also found to have increased when measured by calendar year.

6.5.2 Annual mean adherence to ICS in asthma patients with different patient and lifestyle related variables

In general, females, younger patients, single patients, patients living in the East Midlands, non-smokers, patients with fewer comorbidities and those patient classified with an 'ideal' BMI were found to have lower adherence. These trends were consistent by patient year with a few exceptions. The details of these trends are discussed below.

6.5.2.1 Gender

Mean adherence was slightly higher for the males than females. This trend may be explained by how women use health care, for example, females are more likely to visit a GP [206], which also could explain the observed higher number of females found with asthma in the cohort. A higher proportion of females with asthma were also found to be treated at the higher treatment steps, where patients are at higher risk of asthma exacerbations (Table 6-4).

Table 6-4 The proportion of males and females at each treatment step

	Step 2	Step 3	Step 4	Step 5
male	44.53%	42.43%	41.75%	36.40%
female	55.47%	57.57%	58.25%	63.60%

6.5.2.2 Age

As expected, the youngest two groups of patients (12 to 19 years and 19 to 25 years) were found to have the poorest overall adherence. However, on entering the study, for up to 3 years, the 12 to 19 year olds had a higher mean adherence than the mean for the 19 to 25, 25 to 30 and 35 to 45 year old age brackets.

It is well known that adolescents generally have poor adherence, [128] but the evidence for other age groups is inconsistent in the literature.

The youngest patients in the study may have higher adherence than the slightly older age groups due to parental involvement in patient care and consequentially in their adherence, especially when these youngest patients were first prescribed the medicine especially for the younger part of this group.

However, once patients leave full time education, they lose their prescription payment exemption, which may decrease adherence within the 19-25 year old age group. This is likely to have a higher impact to these patients since they are likely to have a lower income than older asthma patients and are also newly independent from their parents.

6.5.2.3 Marital status

Patients who were single or cohabiting had a lower mean adherence than patients who were recorded as being married, divorced or separated, with those in a stable relationship or widowed patients having the highest adherence. By year 9 of the study, the single patients no longer had the lowest adherence. This may be explained by patients age, where patients who are younger, and associated with lower adherence, were less likely to be married, divorced, separated, in a stable relationship or widowed compared with being single or cohabiting.

Due to this apparent very close, collinear relationship with age, marital status was not included in the modelling or in the relative risk calculations.

6.5.2.4 Region of living

The North East was found to have the highest mean adherence and the South East and East Midlands with the lowest mean adherence recorded.

The lower adherence within the South East and the East midlands may be influenced by the average age or SES of the areas. The population in both regions in 2013 had a higher average disposable income (in 6.5.3 lower SES was found to be associated with lower adherence) than the North East [207] and the North East region

had the highest unemployment rate. [208] The proportion of the population that was over 65 (measured in 2002) was similar in all three regions at 18-18.5%, but the North East had a slightly higher proportion of 50 to 65 year olds (19.7%), which was found in Section 6.4.2 to be associated with higher adherence than in younger patients. [209]

6.5.2.5 Smoking Status

Patients who smoked, or had smoked were found to have a higher adherence than those patients who had never smoked. Very little evidence was found in the literature to associate smoking with adherence, only clinical outcome, where smokers were found to have a higher risk of exacerbation. [55] Patients who smoke may perceive themselves to be at higher risk of exacerbation and consequentially have a greater incentive more adherent, [14] this could be in response to an awareness of the evidence available, or maybe related to experiencing more symptoms of poorly controlled asthma. There is some evidence that smoking affects the efficacy of ICS, making a higher dose necessary, [53 54] therefore a high adherence in smokers may not control symptoms as well as in a non-smoker.

Smoking has also been associated with higher deprivation, [210] where a higher mean adherence was also observed.

6.5.2.6 Comorbidities

Patients with a higher Charlson comorbidity score, meaning that they suffered from more comorbidities, had an associated higher mean adherence. Evidence was presented in Chapter 1 to suggest that patients adherence could be affected by other medicines being prescribed, [80] which is increasingly likely with diagnosed

comorbidities. Very few patients had a score of 15-18, but for these patients the adherence was found to be very high

This effect could be related to patient age, where older patients, who are also likely to have more comorbidities, were found to have a higher adherence. It could also be due to the method of measuring adherence by prescriptions. These patients with comorbidities are likely to have more frequent visits to their GP, where all of their medicine may be prescribed at each or most visits, but not necessarily collected or taken.

6.5.2.7 BMI

Patients with a BMI within the 'ideal' weight range had a lower adherence than patients who were overweight.

There was no available evidence in the literature to support this finding that patients who are classified as overweight were observed to also have a higher risk of exacerbation but the BTS guidelines recommend losing weight to improve asthma outcome. [3] Patients who are overweight may therefore perceive their risk of exacerbation to be higher and are may take their ICS in a more adherent manner. These patients may also have comorbidities that are associated with being overweight such as diabetes or heart disease.

6.5.2.8 Pregnancy

Patients who had a record for being pregnant in a year had a lower mean adherence that the rest of the cohort. In the modelling, the coefficients calculated for the

effect of pregnancy on adherence were not found to be significant; this may be due to the variability of the patients within this subgroup.

Patients who have asthma and were pregnant may have reacted to their asthma differently, some may have been more adherent to keep well, and others may have tried to avoid any 'unnecessary' medicines if they were perceived as harmful potentially to the unborn baby. [211] This effect may also differ by the severity of the patient's asthma, where patients may increase their adherence whilst pregnant if they perceived their risk of exacerbation to be higher. In addition, patients who were pregnant may have had their asthma monitored more closely so adhered more closely.

There is also some evidence that pregnancy in some patients can reduce allergy symptoms, [58] making these patients have a lower requirement for treatment whilst pregnant.

6.5.3 The effect of socioeconomic status related factors on adherence and clinical outcome

In general, the least deprived patients, and patients who did not have a prescription payment exemption were found to have lower adherence. These trends were consistent over patient year with a few exceptions. The details of these trends are discussed below.

The literature showed evidence of higher deprivation being associated with low adherence [63], however, the opposite association was found in the results for this chapter; where patients who lived in areas that are classified as the most deprived had the highest mean adherence.

In the UK, the most deprived patients and patients with some specific comorbidities qualify for prescription payment exemption. Since in this this study, adherence is measured by prescriptions and not medicine taking, the exempt patients could be receiving more of their prescriptions (even if they do not actually fill the prescription or take the medicine) than the non-exempt patients because they have no financial consequence of doing so.

Patients with high deprivation were also found to have more comorbidities, [212] which also make patients more likely to be exempt from co-payment. Additionally, those patients with and comorbidities, and consequently a payment exemption, may have their asthma monitored more closely since they may visit primary care more often, and may be more likely to request prescriptions.

The important factor in a patient's treatment is whether this adherence leads to an improved clinical outcome in these most deprived patients.

6.5.4 The effect of therapy related factors on adherence and clinical outcome

In general, patients who had experienced no adverse effects and patient's prescribed fluticasone or mometasone were found to have lower adherence. These trends were consistent over patient year with a few exceptions. The details of these trends are discussed below.

Patients who experienced no adverse effects had a lower mean adherence than patients who experienced side effects. Patients treated with a higher dose of ICS, to treat more severe asthma, are the patients who were at higher risk of these adverse effects. These patients were also therefore at an increased risk of exacerbation,

making them more likely to perceive adherence as important than patients with less severe asthma. Patients with higher adherence may also be more likely to experience adverse effects simply because they are taking more ICS.

Throughout treatment, those patients taking ciclesonide had the highest recorded adherence, followed by budesonide, then mometasone, where patients who were prescribed fluticasone had a lower mean PPR. From year 4 of recorded treatment, the mean adherence for those patients who were prescribed fluticasone was lower than for all other drug substances. This may be associated with the likelihood of prescribing these different drug substances in different age groups or asthma severity levels, for example ciclesonide is not recommended for patients under 12 years of age, [3] so these younger patients, with lower mean adherence overall may continue to use the ICS that they were prescribed in childhood.

By comparing the proportion of patients within each severity level that were prescribed each drug substance (Table 6-5), the highest proportion of patients prescribed ciclesonide were treated within step 5. The highest proportion of patients treated with fluticasone was for patients treated within step 3. This is consistent with the previous finding that higher adherence is associated with more severe asthma.

Table 6-5. The proportion of patients prescribed each ICS drug substance by treatment step

Step	Beclometasone (%)	Budesonide (%)	Ciclesonide (%)	Mometasone (%)	Fluticasone (%)
2	84.57	9.26	0.19	0.22	7.32
3	32.43	20.86	0.15	0.11	59.33
4	52.57	23.27	0.13	0.09	36.6
5	44.27	17.11	0.47	0.09	48.61
Overall	62.82	16.11	0.16	0.16	28.26

6.5.5 The effect of condition variables on adherence and clinical outcome

In general, patients with good control, at lower treatment steps, and those patients who have not changed step from the previous year, and those patients who have no experienced an exacerbation in the previous year were found to have lower adherence. These trends were consistent over patient year with a few exceptions. The details of these trends are discussed below.

6.5.5.1 Control by SABA use

Patients with poor control had a higher adherence than those patients with low SABA use, used to indicate good control. This is inconsistent with previous studies that have suggested that patients use their SABA in place of using the ICS (rescue medicine rather than preventative therapy). [210] Poor control alongside high ICS adherence, measured by PPR, would suggest that patients, who receive a large amount of SABA, also received all or most of their required quantity of ICS prescriptions. Patients may be prescribed both SABA and ICS inhalers together, making the two measurements of the number of days/ doses prescribed co-dependent. This does not necessarily mean that patients are filling or taking the medicine as prescribed but only receiving the prescriptions, which is a limitation of basing the adherence measure on prescribing data.

Therefore, we are unable to differentiate whether the relationship between poor control and high adherence is caused by patients being treated at a step where their asthma remains extremely uncontrolled despite adherence to their ICS; or because the characteristics of a patient that receives prescription for their SABA

regularly may also make the patient more inclined to receive regular prescriptions for their ICS.

Interestingly, in the data, (not presented) patients who were exempt and were classified as having uncontrolled asthma (higher SABA use) were also found to have higher adherence to ICS than non-exempt patients. This suggests that if a patient is exempt, they receive prescriptions for a higher proportion of their prescribed medicines than non-exempt patients.

6.5.5.2 Treatment step

The evidence presented in Chapter 2 suggested that patients treated at lower treatment steps were likely to have lower adherence, when compared with patients with more serious asthma, treated at step 5, since patients who have more severe asthma, understand the importance of adherence to their prescribed ICS. In addition, patients at higher treatment steps may be monitored more closely. In the analysis, as expected, the adherence for patients treated at steps 2 to 4 were lower than for patients who were treated within step 5.

6.5.5.3 Exacerbation

Patients, who experienced at least 1 exacerbation that was treated within primary or secondary care, generally had a higher mean PPR, than those patients that had not experience an exacerbation. An exception was between years 5-9 of the study for secondary care exacerbations where adherence was lower than for patients who experienced no exacerbation. This is expected to be an anomaly within the data. In this comparison, adherence and outcome were measured over the period, where the duration of the effect that the exacerbation could have had on adherence

would have varied between patients by up to a year. This is a limitation of the methodology.

6.5.6 Strengths and limitations of the methods

The method used to plot mean adherence by time was able to illustrate the overall trend in adherence over time, both by the number of years that a patient had spent in the study and by calendar year. However, the specific causes of any changes could not be determined.

The analysis to investigate the effect of each covariate on adherence was able to show how mean adherence differed between patients with different characteristics, however, the influence of one characteristic, depicted in the study by a variable subgroup, and could have been influenced by other variables acting at the same time, causing a confounding effect on the variable of interest on PPR. For example, the effect of an exacerbation or drug substance prescribed on PPR may be influenced by a patient's asthma severity, where patients with differing severities may have a different effect of an exacerbation. In addition to the effect of the variables included in the study, unmeasurable variables may also have influenced patient adherence. These may include the patients' attitude to treatment for their asthma, where patients may not be more adherent despite any interventions, or those who may be intermittently treated within hospital instead of using preventative treatment prescribed within primary care. There is however little supportive evidence available, but they were considered to be important factors that may affect adherence by medical practitioners consulted.

Another problem in establishing the effect of one variable on another is when they are measure over the same year, especially for time dependent variables. Since we believe that adherence and exacerbation are likely to have a two way relationship, it is difficult to interpret the effect of exacerbation on adherence when they were measure over the same year period, where the exacerbation may have occurred at the start or at the end of the year.

6.6 Conclusion

In this chapter, the effect of each patient characteristic on adherence, measured by PPR, were tested and how time spent in the study period affected mean PPR. Most of the patient variables tested were found to have a statistically significant effect on PPR. However, importantly, many of the patient variables found to be associated with low adherence were also the characteristics that we would expect to make them more likely to have better health and fewer asthma symptoms. Characteristics of note that were found to be related to lower adherence, but could be considered to be associated with better health, included; younger patients, non-smokers, patients with fewer comorbidities, patients with a BMI in the 'healthy' range, lower deprivation, good asthma control and lower asthma severity.

It was also observed that patients who had experienced no exacerbation treated within primary care had lower mean adherence, suggesting that their asthma was likely to be less severe and/ or more controlled. This result is unexpected because if the prescribed ICS' were necessary for these patients to prevent exacerbations, higher adherence would be expected to be associated with fewer exacerbations. However, this relationship was not found to be statistically significant for patients

who required secondary care to treat more severe exacerbations. These inconsistencies may be explained by the adherence and clinical outcome in this analysis being measured over the same annual period. Both primary and secondary care exacerbations are thought to influence adherence, but a patient experiencing an exacerbation would also be expected to be influenced by adherence. Therefore, the causal relationship between these variables is complex and further work to study the effect of the previous year's adherence and clinical outcome to try to understand the causal relationship is required (Chapter 7).

The effect of the subgroups of the patient variables on mean PPR was found to be reasonably consistent over time, including patient age at each year, region of registered practice, and treatment step. However, the trend in PPR in some subgroups was inconsistent over time since entering the study where some subgroups had a different trend to others including:

- PPR measured in year 1 was higher in the youngest age group than the groups up to 45 years. The PPR measured in the other follow up patient years of the youngest age group remained higher than the 20-25 year old age group.
- The mean PPR measure in patients registered in the East Midlands was the lowest, but increased over time to become the highest.
- The annual mean PPR measured in the patients treated at step 2 each year (lowest severity of asthma included in the study), was the lowest of all the subgroups for treatment steps in the first year, but it increased over time to become 2nd highest, just behind the step 5 patients.

These results have shown that the relationship between the variables studied and adherence is complex. Further analysis that considers the individual contribution of each patient variable to PPR while adjusting for the effect of others (confounders) would make it easier to establish which characteristics have a large influence on adherence. Multivariate regression can be used to make this comparison, where the simultaneous effect of the patient variables on a dependent variable (PPR in this case) can be determined. This was investigated in Chapter 8.

Chapter 7 Association between adherence to ICS and asthma exacerbation

7.1 Introduction

In Chapter 6, a complex relationship was found between patient adherence and whether the patient experienced an exacerbation. Many of the characteristics associated with low adherence to ICS in asthma patients were also the characteristics associated with better health and fewer asthma symptoms. Counterintuitively, this questions the necessity or the appropriateness of adherence to an ICS for asthma patients. Therefore it is important to understand the association between adherence to a prescribed ICS regimen on the asthma patient's outcome, measured by exacerbation occurrence. The methods used in this chapter have been used previously in epidemiological studies across many diseases, including asthma. Many previous studies have found a link between good adherence and outcome in asthma, [76 118] however, many retrospective adherence studies in asthma did not prove this concept and instead directly hypothesised that good adherence would lead to optimal outcomes (Appendix 4).

It is hypothesised that there will be a significant increase in PPR measured after exacerbation from the level prior to exacerbation, and patients with higher adherence are expected to be less likely to experience an exacerbation. The guidelines state that "prior to discharge, trained staff should give asthma education" [3] which would be expected to improve adherence to some extent. Patients who experience an exacerbation would be also be considered to have more uncontrolled asthma, either because they were non adherent to their prescribed ICS or because they were not treated at a high enough step of the 2014 BTS/ SIGN guidelines. [56] In both of these

cases, adherence would be expected to increase since patients with more severe asthma are reported to have higher adherence [213] and patients with poor asthma control and adherence are likely to be identified to need an intervention to improve their adherence, such as at hospital discharge. [214] Patients with higher adherence would also be expected to be less likely to experience an exacerbation.

The association between adherence and exacerbation was investigated from both directions, i.e. evaluating the effect of exacerbation on whether the patient had an optimal adherence to ICS, and the effect of adherence on whether a patient experienced an exacerbation. Therefore, the adherence or exacerbation, measured over the previous year and over the same year were both considered.

The level of adherence that on average a patient must drop below before poor adherence effects clinical outcome was then determined by comparing the relative risk of exacerbation at different levels of adherence. The relative risk of exposure, compared with non-exposure is a method commonly used in epidemiology [215], where the exposure in this application is when the patient is exposed to below a percentage level of PPR. Using the appropriate cut off level for adherence, the continuous adherence variable converted adherence into a dichotomous variable, to represent whether a level of adherence is likely to influence outcome. This variable was then used to enable the effect of adherence on clinical outcome over time to be investigated to compare the three continuous variables.

7.2 Aim and objectives

This chapter investigates the temporal relationship between adherence to ICS and exacerbations of asthma to examine the hypothesis supporting their association. The objectives included:

- To investigate the effect of an exacerbation event on adherence to ICS.
- To investigate the effect correlation between annual prevalence of exacerbation and PPR measure in the same and the previous year.
- To estimate the relative risk of an exacerbation at different levels of adherence to ICS.
- To examine the association between adherence to ICS and an exacerbation of asthma over time

7.3 Methods

7.3.1 Study design and data sources

This cohort study used data from the CPRD and HES. The variables for measuring adherence (Chapter 4), patient asthma outcomes (Chapter 5) and patient variables for the study cohort (Chapter 3) in each calendar year were previously defined and identified. A variable to indicate the number of years that the patient had been followed in the study (the 'patient year') was also included in the analysis.

7.3.2 Mean PPR before and after the first exacerbation

This analysis took a before-and-after comparison approach to evaluate the changes of adherence to ICS measured before and after the first asthma exacerbation event observed during study period for each patient, i.e. the PPR for the year immediately before and the year after each patient's first exacerbation were compared.

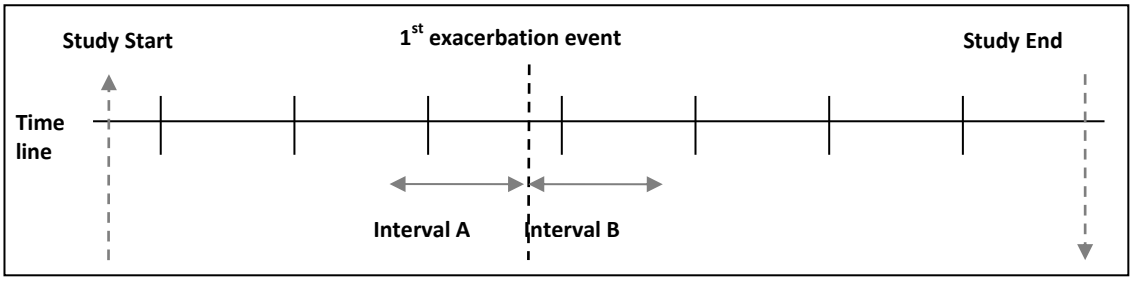
A year interval was chosen to remove the effect of patients being prescribed several months of medicine at each prescription and also not reduce the effects of any seasonal variation, however, a shorter time period, or multiple consecutive time periods could be used, to enable the observation of any changes in adherence immediately and in the consecutive 6 month periods before and after an exacerbation.

Patients who received at least one ICS prescription in the year before and after their first recorded exacerbation, were included in this analysis, since PPR could not be measured if no ICS had been prescribed.

Each patient's first exacerbation event within the study period was identified at two different levels of severity; when only primary care treatment was required (lowest), where the patient required secondary care treatment (highest), and a combined level where severity was not considered (either primary or secondary care treatment needed) as identified within Chapter 5. This created 3 dates for each patient for their first exacerbation within primary care, secondary care and another variable repeating for the earliest one occurring of these two dates.

For each individual patient, a PPR was calculated in two 12 month periods immediately before and after the patients first recorded exacerbation i.e. PPR was measured in two consecutive one year intervals, where the end date of the first interval and the start date of the second interval coincide with the date of the patient's first exacerbation (Figure 7-1). The 2 consecutive adherence intervals were calculated separately for each level of exacerbation severity. Mean PPR before and after the exacerbation were compared using a Wilcoxon signed rank sum test.

Figure 7-1. Conceptual framework for the timeframe of PPR calculation in the year before and after exacerbation



7.3.3 The annual prevalence of exacerbation against PPR

The annual proportion of patients who experienced an exacerbation in each patient year are presented on a scatter plot against adherence (rounded to the whole number percentage point) measured over the same year period. This approach was repeated to compare the prevalence of exacerbation occurrence with adherence measured over the previous year. A trend line was included to aid interpretation of the results.

7.3.4 Relative risk of an exacerbation at different levels of PPR measured in the same or previous year

The relative risk of an exacerbation occurring was calculated separately for patients who had an exacerbation recorded within primary or secondary care, for patients with a PPR measured at below, or above each cut off level. The relative risk was calculated at PPR cut off levels at 10% intervals between 0% and 100%, both for PPR measured in the same year and in the previous year to the outcome measure.

The different exposure groups were defined as whether the patients' adherence was above or below each level of PPR over each year interval. The relative risk was calculated at PPR intervals of 10%. The occurrence of an exacerbation was used as the outcome. The relative risk calculated is described in Table 7-1.

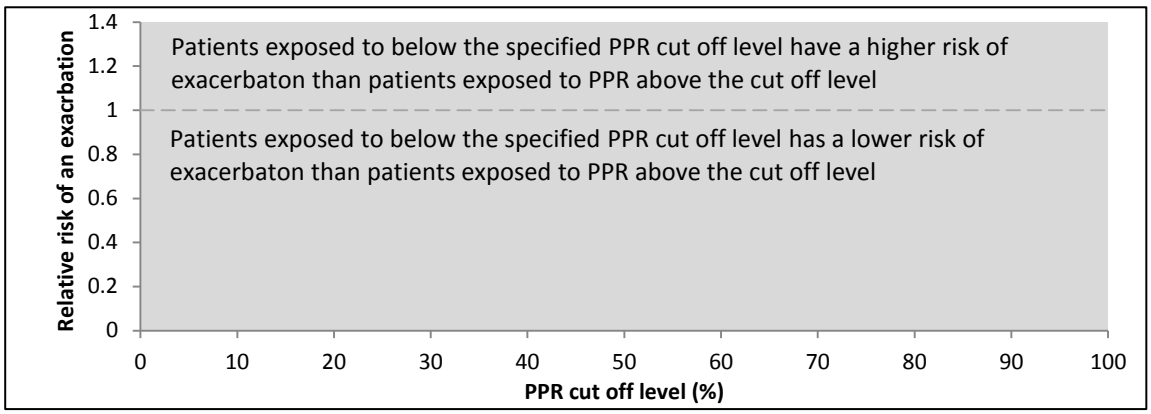
Table 7-1. Relative risk calculation

		Outcome		
		Exacerbation	No Exacerbation	Total patients
Exposure	<% PPR	Number of patients (a)	Number of patients (b)	a+b
	>=% PPR	Number of patients (c)	Number of patients (d)	c+d

$$\textbf{Relative risk} = \frac{a/a+b}{c/c+d}$$

A relative risk equal to 1 indicates that there is no difference in risk between the two groups. If the relative risk is more than 1, the group exposed to below the specified level of PPR has a higher risk of exacerbation than the group exposed to a PPR of above this level. If the relative risk is less than 1, the group exposed to below the specified level of PPR has a lower risk of exacerbation than the group exposed to a PPR of above this level.

Figure 7-2. Interpretation of the the relative risk for patients, by PPR cut off level



Relative risk is increased for a subgroup if it either:

- The variable subgroup has a higher exacerbation rate in the patient group with a PPR below the cut off level
- The variable subgroup has a lower exacerbation rate in the patient group with a PPR above the cut off level

The results for the relative risk of a patient experiencing an exacerbation, using 10% interval cut off level of PPR were plotted for each 10% PPR cut off, repeated for each severity of exacerbation. The graphs were used to identify the effect of adherence on exacerbation rate and to identify any level of PPR that appeared to effect exacerbation in the patients.

7.3.5 Trend of PPR over time in relation to exacerbation

In Chapter 6, the trend over time for the mean PPR for patients who had and hadn't experienced an exacerbation were presented for an exacerbation recorded in the same year as adherence was measured. In this chapter, the mean adherence for patients who experienced an exacerbation in the previous year to when adherence was measured, will be calculated and presented graphically.

The trend over time for the effect of adherence on clinical outcome was also investigated by calculating the mean exacerbation occurrence across patients with a PPR above or below the selected cut off level identified by the relative risk analysis. The percentage of patients who experienced an exacerbation (y axis) was calculated separately for patients with above and below the selected cut off level of adherence and plotted against the number of years that the patients had been included in the study (x axis) to assess changes over time.

7.4 Results

7.4.1 Mean PPR before and after the first exacerbation

The PPR measured in the year immediately after the exacerbation event was significantly higher than the PPR measured in the previous year to the exacerbation.

This was true for the first exacerbations recorded from either the primary or secondary care data during the study period.

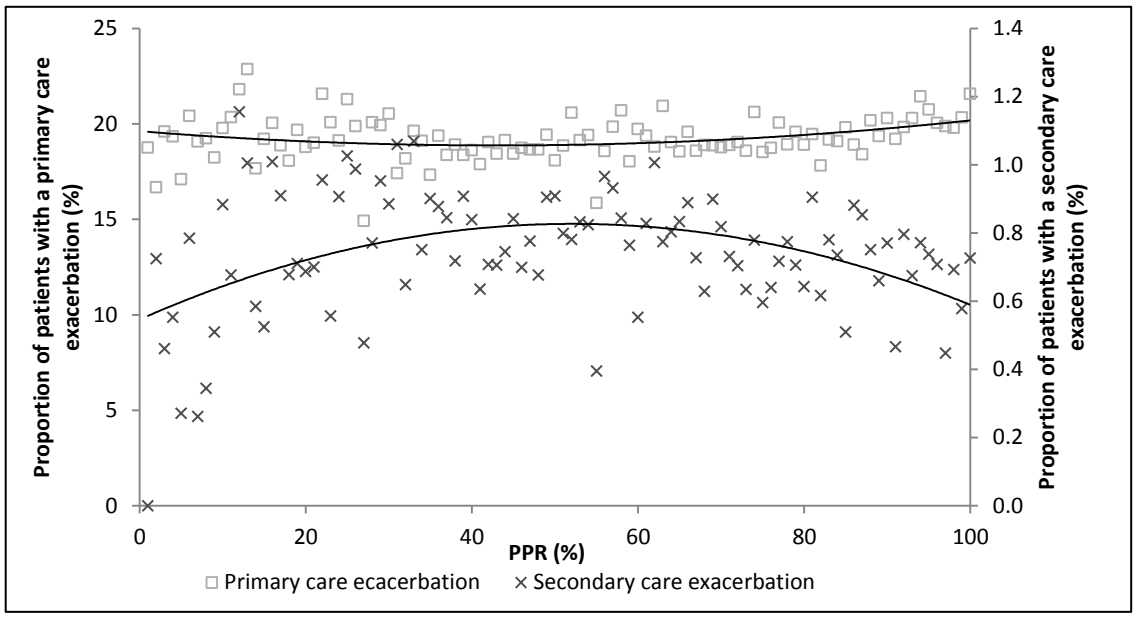
Table 7-2. Mean PPR measured before and after patients' first exacerbation

Exacerbation severity	Observations		Mean PPR (%)	Std. Dev	P value
Primary	67369	before exacerbation	51.57	33.93	<0.0001
		after exacerbation	58.96	33.46	
Secondary	2195	before exacerbation	66.42	29.14	0.0001
		after exacerbation	69.21	29.58	
Combined	67014	before exacerbation	51.68	33.92	<0.0001
		after exacerbation	59.01	33.45	

7.4.2 Annual prevalence of exacerbation against PPR measured in the prior year and same year

The mean proportion of patients who experienced an exacerbation recorded in primary care in the same year remained consistent across different PPR levels. The proportion of the cohort at each level of PPR, who had an exacerbation recorded in secondary care increased with increasing PPR up to a PPR of approximately 50%, but then generally decreased for patients with a PPR up to 100% (Figure 7.3).

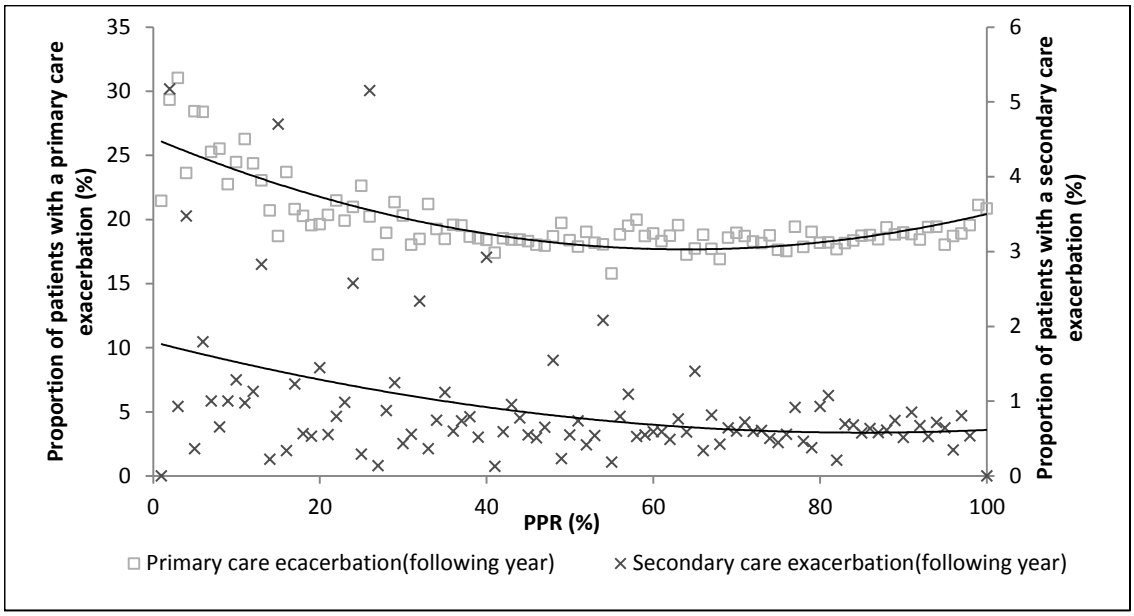
Figure 7-3. Proportion of patients who experienced an exacerbation by different PPR levels (measured in the same year)



The proportion of patients who experienced an exacerbation, at each PPR level measured over the previous year, decreased with increasing PPR up to approximately 50% PPR. Above 50% PPR, the proportion of patients who experienced either an exacerbation which required primary of secondary care remained reasonably constant. A slight increase in exacerbations treated within primary care was noted for the patients at the highest percentage PPR (Figure 7-4).

The proportion of patients observed at each PPR level was lower when the previous year's PPR values were compared with the clinical outcome, than the same years PPR values were used. This is caused by fewer patients meeting the requirement for at least 2 years of data for each patient. It is likely that patients with a longer requirement for ICS would also have a higher risk of exacerbation.

Figure 7-4. Proportion of patients who experienced an exacerbation by different PPR levels (measured in previous year)

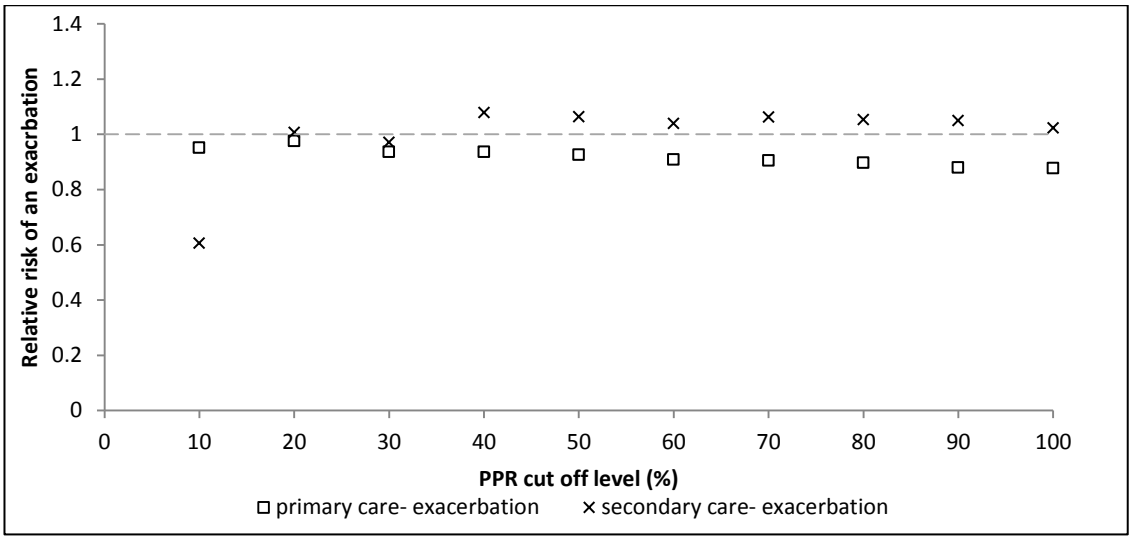


7.4.3 Relative risk of exacerbation, following exposure to different levels of PPR in the previous year

Surprisingly those patients, who were exposed to below each PPR cut off level, had a lower risk of experiencing an exacerbation requiring treatment within primary care than patients with a PPR above each level. This is shown by the relative risk being below 1 (Figure 7-5).

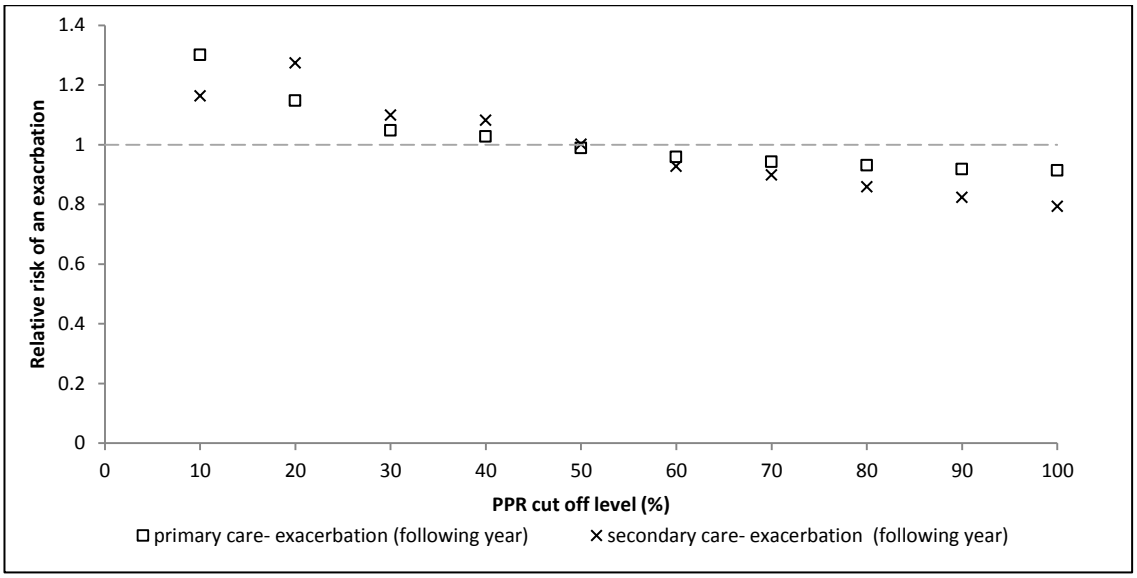
Similarly, patients with below 10% to 30% PPR also had a lower risk of an exacerbation treated within secondary care than those patients with a PPR above this level. However, for the cut off levels at 40% PPR and above, the risk of experiencing an exacerbation was greater than 1, meaning that the risk of exacerbation was higher for patients with a PPR below each of the cut off levels.

Figure 7-5. Relative risk for patients to experience an exacerbation, by different PPR cut off levels (measured over the same year)



When PPR was measured in the previous year to when exacerbation occurrence was measured, patients who were exposed to a PPR of below each cut off level up to 50%, had a higher risk of exacerbation than patients who had a PPR above this cut off level. At the 50% cut off level, the risk changed, where the patients with a PPR above 60% had the higher risk of exacerbation than those with a PPR below 60%. This trend was more pronounced for those patients who had an exacerbation recorded that was treated within secondary care rather than primary care (Figure 7-6).

Figure 7-6. Relative risk for patients to experience an exacerbation, by different PPR levels (measured over the previous year)

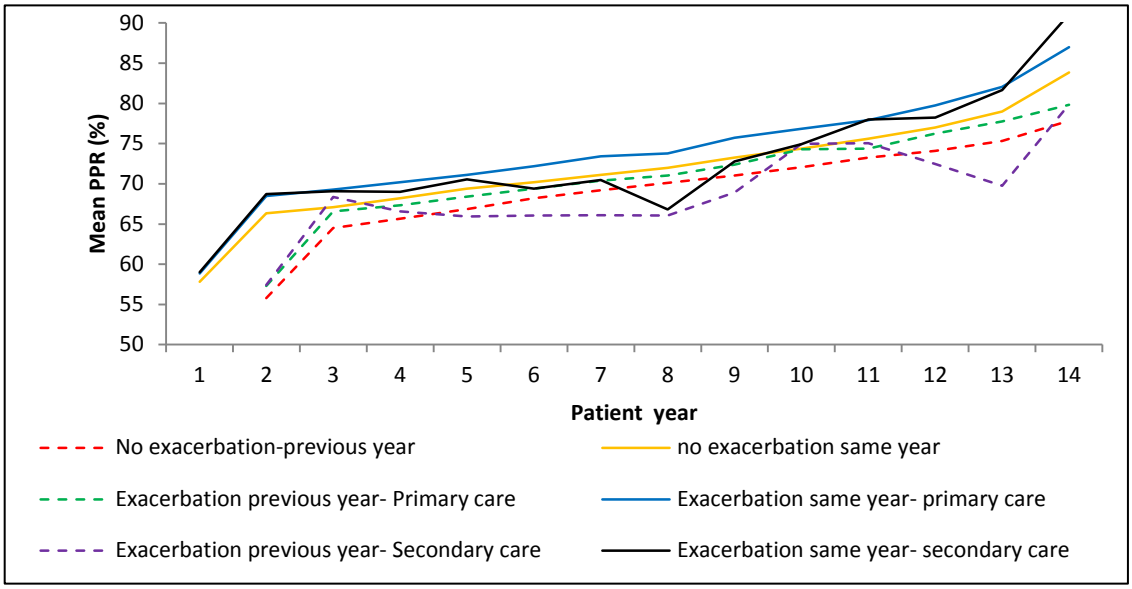


The risk of experiencing an exacerbation, when measured in the following year at the 50% PPR cut off level was equal if a patient's PPR was above or below the 50% cut off. For all PPR cut off levels below 50%, those patients with a PPR below the specified cut off level had a higher risk of exacerbation, than patients with a PPR above the cut off level.

7.4.4 Trend of mean PPR in each patient year stratified by exacerbation occurrence in the same year or prior year

Over the study period patients who had experienced an exacerbation, treated within primary care during the same or the previous year, had a consistently higher mean PPR than those patients that had not experience an exacerbation. No consistent trend was noted for exacerbations treated within secondary care. Mean PPR was higher for patients who experienced an exacerbation in the same year than those who had experienced an exacerbation in the previous year (Figure 7-7).

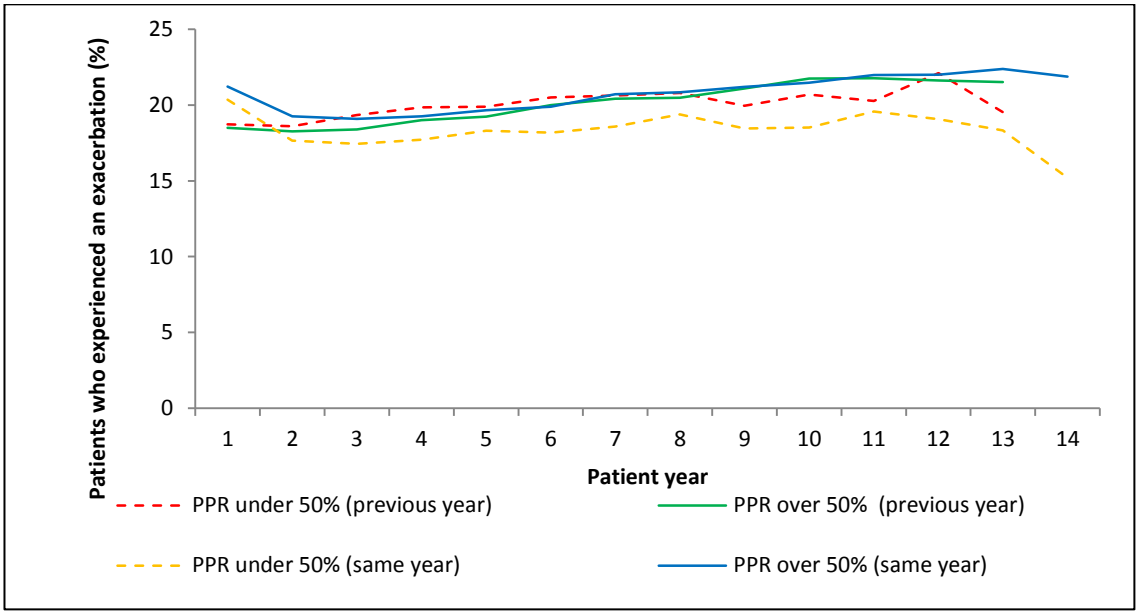
Figure 7-7. Trend of mean PPR in each patient year stratified by exacerbation occurrence(measured in the same or the previous year)



Throughout the study period, a higher proportion of patients with a PPR of over 50% experienced an exacerbation within primary care than those patients with a PPR of below 50% when measure over the same year.

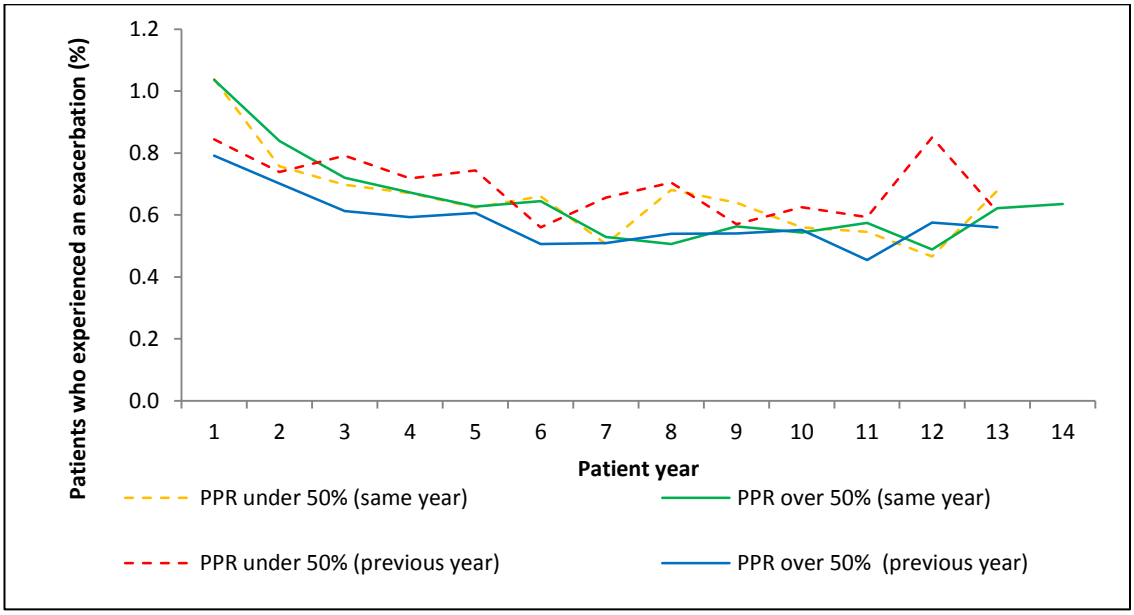
When PPR was measured over the previous year to the exacerbation occurrence, treated within primary care, the trend in the effect of PPR above or below 50% PPR on exacerbation was inconsistent over time (Figure 7-8).

Figure 7-8. Proportion of patients who experienced an exacerbation treated within primary care stratified by mean PPR over or less than 50% (measured in the same year or previous years)



When PPR was measured in the same year as a patient had experienced an exacerbation treated within secondary care, no consistent trend was found in the proportion of patients who experienced an exacerbation between the patients with above or below 50% PPR. But when the effect of PPR in the previous year was used, the proportion of patients who used secondary care to treat an exacerbation was consistently higher in the group with below 50% PPR (Figure 7-9).

Figure 7-9. Proportion of patients who experienced an exacerbation treated within secondary care stratified by mean PPR over or less than 50% (measured in the same year or previous years)



7.5 Discussion

The results of this study confirmed a complex relationship between adherence to ICS and exacerbations of asthma; it is discussed from two directions; the effect of outcome on adherence to understand the effect of a patient's previous outcome on their future adherence and the effect of adherence on outcome to illustrate the importance of adherence on a patient's outcome.

7.5.1 The effect of exacerbation on adherence

The effect of an exacerbation on adherence was investigated using two approaches, including comparing the mean PPR in the year before and after an exacerbation (Section 7.4.1), and presenting the trend of mean annual PPR in patients who had and hadn't experienced an exacerbation (Section 7.4.4).

As expected the before and after analysis showed a clear increase in PPR with the occurrence of an exacerbation. A patient's PPR is expected to improve following an

exacerbation, due to several reasons including their attitude towards their need for treatment and patients who may be identified as requiring an intervention to improve their adherence [214] However, it is difficult to tell whether the low PPR before the exacerbation was the cause of the exacerbation or if the exacerbation caused the increase in PPR.

Exacerbations recorded within primary care measured over the same or the previous year to PPR were associated with increased PPR throughout the study period when compared with patients who hadn't experienced an exacerbation, but the results for exacerbations treated within secondary care were not so consistent over time. There are many possible explanations for this observation.

In the before and after analysis mean PPR in the year before a primary care exacerbation started off lower than before a secondary care exacerbation- this indicates that patients with worsening asthma had already increased their adherence. The patients who were more likely to require secondary care treatment had more severe asthma which may also have made them more likely to adhere to their prescribed ICS. These patients may have experience exacerbations that required hospitalisation, despite their good adherence to their prescribed asthma treatments.

The inconsistent results in the trend in mean PPR by exacerbation occurrence could be explained by patients having unrecorded ICS prescribed to them whilst they are in hospital and on discharge. This could cause a lower PPR to be calculated, especially when measured over the same year duration as exacerbation. Patients who were treated within primary care to treat an exacerbation may have also been prescribed

more than one ICS at the same time and also may have received interventions to improve their adherence and/ or asthma control.

The inconsistent results in the secondary care data may also have been caused by method limitations. For example, the low number of patients treated within secondary care; when these patients were subdivided by patient year the patient numbers were lower especially for patients at a greater number of years in the study. Another explanation could be due to the differences in the risk and severity of exacerbation between patients with different characteristics, where PPR may be co-dependent with other patient variables such as severity of asthma, comorbidities or age.

Since an exacerbation was found to have an increasing effect on PPR in the PPR before and after analysis, it was also expected that PPR in the year following an exacerbation to be greater than when PPR and exacerbation occurrence were measured over the same year, however, this was not observed. Mean PPR was also found to be higher when it was measured during the same year as exacerbation occurrence than when exacerbation occurrence from the previous year was used.

This could be explained by patient exacerbations that occurred at the end of the annual period, which would not have caused the expected elevation in mean PPR as much as if the exacerbation occurred at the beginning of the year or in the year before. However, the increasing effect of an exacerbation on PPR may only be temporary. If this increasing effects lasts for less than a year this may explain why the effect of an exacerbation on PPR in the previous year was less that when it occurred in the same year.

7.5.2 The effect of adherence on exacerbation

In the first approach used to measure the effect of adherence on exacerbation, where PPR was measured over the previous year to exacerbation occurrence, as expected, exacerbation decreased with increasing adherence. However, the results were not consistent for exacerbations measured over the same year as PPR.

An exception to this was at a PPR of approximately 80%-100%, where the proportion of exacerbations requiring treatment within primary care (measured in the year after the PPR was measured) increased. This may have been due to patients who had high adherence were also more likely to visit primary care for an exacerbation, since these patients were likely to be more regular attenders at primary care, and may seek help earlier to control an exacerbation of their asthma. This reinforces the idea that the occurrence of an exacerbation treated within primary care, is partially influenced by how likely to the patient is to visit primary care rather entirely associated with how poor their clinical outcome was.

When PPR and the patient's clinical outcome were measured over the same year, unexpected results were found, where the proportion of patients who experienced an exacerbation treated within secondary care was lower at the extremes of PPR recorded 0% and 100% PPR. Little effect of PPR on exacerbation occurrence was observed for exacerbations treated within primary care. By measuring the variables in the same year, we are unable to identify how much of the PPR measure is effected by the timing of the exacerbation within the year, making these results difficult to interpret.

When using the relative risk analysis, where PPR was measured in the previous year to exacerbation occurrence, the relative risk of a patient experiencing an exacerbation was higher if they had a PPR of below the cut off level rather than above the cut off level, up to a cut off level of PPR of approximately 50%. As the cut off level increased above 50%, patients with a PPR below the cut of levels had a decreasing risk of an exacerbation. This means that at higher cut off levels, the mean advantage of having a PPR above e.g. 60% or 70% (compared with having a PPR below this level, maybe 50%) did not appear to influence patient outcome.

The relative risk of experiencing a primary care exacerbation in the same year as PPR was measured, gave unexpected results, where patient risk was higher with a PPR below rather than above each cut off level.

On average across all patients an increase in PPR above 50% appears to make little difference to clinical outcome. Therefore 50% appears to be clinically relevant for this data and method of calculating PPR, and was used to compare the effect of below or above this level of PPR on exacerbation over time.

In the trend over time analysis, over time spent in the study period, the results for the effect of PPR on exacerbations measured within primary or secondary care, over the same or the previous year were inconsistent.

Patients with a PPR of over 50% were found to have a higher risk of primary care exacerbation than the subgroup of patients with under 50% PPR when measured over the same year. This unexpected result may be explained by the slight increase in the proportion of patients who experienced an exacerbation in those patients with above 90% PPR (

Figure 7-3 and Figure 7-4). As described in Section 7.5.2, this may be caused by the patients with more severe asthma or comorbidities attending primary care more often and consequently having higher adherence and seeking help early for exacerbations.

No consistent effect was observed for the effect of adherence on secondary care exacerbations, when measured in the same year, but when PPR was measured over the previous year, as expected a higher proportion of patients with under 50% PPR experienced an exacerbation.

7.5.3 Strengths and limitations of the methods

Where the time dependent variables were measured in the same year it is difficult to determine causality, for example in this case, whether an exacerbation that occurred early in the year had caused the PPR to be higher or if the PPR occurred late in the year, whether the PPR was higher prior to the exacerbation. For this reason, the effect of the previous year's exacerbation occurrence on adherence and the previous year's adherence on exacerbation were also compared. However as discussed in the previous section, this could create a different problem due to the persistence of the effect of an exacerbation or the persistence of the effect of a level of adherence which may not have a long enough duration to influence the adherence or exacerbation occurrence in the following year. Therefore, in further analysis, both the variables in the same year and the previous year for adherence and clinical outcome should be considered.

The methods used in this chapter did not take into account other measurable and unmeasurable patient variables that may affect the relationship between PPR and exacerbation. In Chapter 6, many of the measurable variables such as severity of asthma or gender were found were found to influence mean PPR when used to

subgroup the patients, and many may also have caused differences in the relationship between PPR and exacerbation. For instance, the effect of a secondary care exacerbation in the previous year was not found to have a significant effect on PPR, but this may have been masked by differences in exacerbation in patients with different severities of asthma.

This method of using the relative risk to investigate the effect of PPR levels on exacerbation risk was useful to identify a 'population level' PPR cut off, where if patients are exposed to a PPR below this level, on average they have an increased risk of exacerbation compared with patients with a PPR above this level. But this method is reasonably difficult to interpret, since a higher relative risk of adherence being below each cut off level could have been either due to a higher risk of an exacerbation in the patients who were exposed to below the cut off level of PPR or a decrease in the risk for patients who were exposed to above the cut off level of PPR. When interpreting the results for relative risk, both of these possible causes must be considered. Additionally, this cut off level is for the mean effect of adherence on exacerbation across the population, so may not be appropriate to apply the findings at an individual patient level since patients may have characteristics that may make them higher or lower risk than the average for the population. Therefore, the clinically significant level of 50% adherence found in this chapter cannot be directly translated into a recommendation that patients only need 50% adherence to achieve their best possible clinical outcome, since it is only appropriate to the method of measuring adherence used in this study, since different methods and data are likely to provide different measured adherence levels. In this study prescribing data was used which may

overestimate patient adherence. Patient's characteristics such as severity of asthma could also influence this adherence significance level, since the 50% adherence level calculated was an average across all patients, we cannot apply this result to individual patients.

7.6 Conclusion

This chapter has generally confirmed the expectation that the occurrence of an exacerbation would lead to higher adherence, and that an increase in adherence would lead to a decrease in the chance of a patient experiencing an exacerbation of asthma especially when measured in the previous year. However, patients with the highest adherence rates (90-100%) also had a higher chance of seeking treatment for an exacerbation within primary care.

As expected we have also seen that patients exposed to below a mean of 50% PPR (compared with above 50% PPR) had a higher risk of experiencing exacerbation that required treatment within secondary care, when measured over the previous year, but results were less consistent for the other results (primary care, and secondary care same year) and were reversed for exacerbations treated within primary care when measured in the same year. This may be related to the differing effects of other patient characteristics such as asthma severity or comorbidities.

This analysis highlighted the importance of considering the effect of the time dependent variables, measured over the previous year, on adherence. In addition, the persistence of the time dependent variables must be considered, i.e. how much they change over time. Therefore, when modelling the effect of multiple variables on PPR we must also include adherence and exacerbation occurrence measured in the same

and the year before the PPR was measured. This allows for effects of previous PPR and clinical outcome on PPR to be assessed, i.e. the persistence of PPR and the effect of previous poor outcome.

Chapter 8 Modelling annual prescription possession ratio of inhaled corticosteroids over time and adjusting for multiple patient variables

8.1 Introduction

The approaches used in the previous chapters to understand the effects of patient variables on adherence identified many patients characteristics associated with lower adherence. Some of the effects of these characteristics tested were found to change over time. In addition both previous adherence and previous exacerbations were found to affect a patient's adherence to ICS.

However, the approaches used were found to have two main limitations; the methods used to understand the effect on mean adherence between patients with different characteristics did not take into account other measurable and unmeasurable patient variables that may have affected the relationship between PPR and exacerbation, and when the time dependent variables were measured in the same year, causality is difficult to determine.

It is important to consider these limitations and to study the effect of variables on adherence further since unexpectedly in the previous chapters it was found that less severe asthma or better health was found to be more likely be associated with poorer adherence.

In this chapter an alternative method was trialled, using a regression model, to determine the individual effects of a patient characteristic on adherence, while also taking into account the effects of multiple other characteristics including time.

Since in chapter 7 it was found that adherence may have a relationship with past adherence, the effect of previous adherence ideally needed to be included in the model as a covariate. In Chapter 7, it was also found to be difficult to interpret the effect of an exacerbation on adherence when they were both measured over the same time period since adherence is measured as an average over the whole year, so we cannot determine if the adherence level measured was influenced before or after an exacerbation occurred, therefore clinical outcome measured over the previous year was also included in the model to allow the effect of exacerbation on adherence occurring in the following year to also be observed. Clinical outcome was therefore included in the model separately as a measurement taken during the same and during the previous year as adherence was measured. Since both measures were found to effect adherence in the two way analysis in Chapter 7 (Figure 7-7, 224), especially for those exacerbations treated within primary care. If the exacerbations measured during the same year were excluded from the model we would not be able to also include any short term effects of exacerbation occurrence in the model.

As well as the effect of poor patient outcome on adherence, it was also believed that adherence would affect outcome, i.e. a two way relationship between adherence and clinical outcome was expected. This raises two complications when using regression; autocorrelation (correlation between adherence and its previous values) and simultaneity were the dependent variable adherence and the another variable (in this case, clinical outcome) influence each other at the same time.

Therefore, to obtain reliable estimates of the effect of different variables on adherence, a simple regression model could not be used; instead, a more complex dynamic panel model was required as well as a more complex technique for estimation, such methods have been commonly used in econometrics.

8.2 Aim

This chapter aimed to model asthma patients adherence to ICS over time, adjusting for patient variables. The objectives included:

- To select an appropriate dynamic panel model and to identify an appropriate estimator to model patients' adherence, to ICS over time
- To explore the association between asthma patients adherence to ICS and variables including patients' characteristics, previous adherence to ICS and clinical outcomes.

8.3 Method

In order to determine the effect of each of the selected variables on adherence to ICS by PPR, first a model must be defined, and then an appropriate method must be selected to estimate the effect of each variable in the model.

8.3.1 Data source

The variables to be used in this chapter were derived from the CPRD data for each patient in the cohort by calendar year for adherence, patient asthma outcomes, patient variables (developed in Chapters 3, 4 and 5) and a variable to indicate the number of years that the patient had been followed in the study (the 'patient year').

Based on the findings from the previous chapters where the effect of these variables on adherence were investigated, the variables to be included in the multivariate regression model were chosen, summarised in Table 8-1 and discussed below.

Table 8-1. Variables to be included in the model

Variable subgroup	variable name	Time dependent	Variable included in the model
Patient	Region of living	No	No
	Marital status	No	No
	Gender	No	Yes
	Age in years	Yes	Yes
	Smoking	Yes	Yes
	Co-morbidities	No	Yes
	Pregnancy	Yes	Yes
	BMI	Yes	No
Deprivation	Deprivation status	No	Yes
	Prescription exemption	No	Yes
Condition	Severity of Asthma	Yes	Yes
	Change in step from previous year	Yes	Yes
	Asthma control	Yes	Yes
	Primary care exacerbation (same year)	Yes	Yes
	Secondary care exacerbation (same year)	Yes	Yes
	Primary care exacerbation (previous year)	Yes	Yes
	Secondary care exacerbation (previous year)	Yes	Yes
	Years in study (duration of treatment)	Yes	Yes
Therapy	Adverse effects from ICS/OCS	Yes	No
	Drug substance	Yes	Yes
	Previous adherence	Yes	Yes

Patients who had never smoked were found to have a lower mean adherence than those who had smoked (Chapter 6), however, the results for patients who smoked or had previously smoked were very similar, therefore, and the variable was grouped for future analysis to produce an ever smoked dummy variable.

The variable for BMI in the CPRD had large amounts of missing data. This reduced the size of the cohort available for analysis (Chapter 6) and led to the increased

variation between subgroups, meaning that no consistent trend over time could be found. Therefore, BMI was not included in the models of adherence in this study.

Adverse effects were also not included in the model, because the low number of patients with an adverse event recorded would reduce the chance of a significant effect being observed on the measured adherence. Additionally, the occurrence of an adverse event was found to be closely associated with those patients with either a high use of ICS (associated with higher adherence) or a higher dose prescribed, associated with patients with a higher severity of asthma, which was also found to be associated with higher adherence.

Some variables derived from the CPRD data were not time dependent. These variables could not be included in the modelling since any variables that are consistent over time are lost during the modelling calculations (during first differencing). To consider the effect of these variables, the model must be repeated for subgroups of the cohort for each time dependent characteristic. Four time invariant variables were chosen to be used; gender, deprivation, comorbidities and prescription exemption. The variables for a patient's relationship status and region of living were not chosen to be included.

A patient's relationship status was found to affect adherence (Chapter 6), where being married generally had a higher mean adherence than the group of patients who were recorded as being single, and patients who were divorced or separated had a similar adherence to the married patients. This is likely to be associated with an increased likelihood of a patient being classified as single if they are younger or older in age, if they are classified as being married or separated. This variable also

has many subcategories, which are difficult to combine. In addition, over the period of the study, for some patients the relationship status is likely to change, which was not captured in the data.

Very little evidence in the literature search carried out was found to associate region of living with adherence to ICS. In the analysis in Chapter 6 only some small differences were observed between regions in the cross-sectional analysis and the trends observed were not consistent across the study period. With 10 different regions recorded in the CPRD, and the small differences observed between the groups, inferences about an effect of region on PPR in the model are likely to be difficult to make, and is not the focus for this study.

8.3.2 Model selection

A panel data model was constructed to assess the dynamic changes in adherence to ICS (measured by PPR) over time as well as its relationship with asthma clinical outcomes and other patient variables, described in the following equation.

$$PPR_{it} = \alpha PPR_{i,t-1} + \gamma Y_{it} + \beta_0 + \beta_1 X_{1it} + \ldots + \beta_k X_{kit} + \lambda_i + U_{it} \qquad \textbf{Equation 8.1}$$

where indexes *i*=1,…,N patients and *t*=1,…,t time periods.

The coefficients included:

- α: the coefficient of the lagged dependent variable PPR_{-1} that represents any dynamic relationships PPR may have with previous PPR.
- γ: the coefficient of Y that represents the relationship between clinical outcome and PPR.
- (β_0, β_1…, β_k); a set of coefficients on a set of independent regressors (patient variables)(X_1, X_2…, X_k), including a lagged clinical outcome to capture the effect

of previous poor clinical outcome on PPR, and a variable for time since the patient entered the study.

- λ: the unmeasured patient-specific effect on PPR that does not vary over time (fixed effect).
- U; the error term that can vary over patients and time, (the time varying error or idiosyncratic error). The error term U can be heteroscedastic, (its variance can be unequal over time), and auto correlated (its value can be correlated over time).

8.3.3 Method to estimate the model

To select appropriate estimators for the model, the characteristics of the variables to be included in the model needed to be considered. These included:

1) Problems with endogeneity (the effect of unmeasured factors on the dependent variable) are expected to be present, which can vary between patients and over time. This is captured in the idiosyncratic error (U) term. This can be caused by measurement error, omitted variables, or simultaneity. [216]
    a) Omitted variables, when some patient variables cannot be included in the model but may be correlated with the other explanatory variables. This would include patient variables that may influence their adherence, but cannot be measured in the CPRD e.g. their belief about their asthma.
    b) Simultaneity is when an independent variable, for example clinical outcome and the dependent variable (adherence) were shown to have a two-way relationship (Chapter 7), clinical outcome was shown to affect adherence,

and adherence was shown to affect clinical outcome, illustrated in the following equation.

$$PPR_{it} = Y_{0+}\gamma_1 Y_{it} + U_{it} \quad \text{and} \quad Y_{it} = \alpha_{0+}\alpha_1 PPR_{it} + V_{it} \qquad \textbf{Equation 8.2}$$

Indexes i=1,…,N patients and t=1,…,T time periods.
γ: the coefficient of Y that represents clinical outcome
α: the coefficient of PPR

2) Autocorrelation in PPR over time was expected to be present where the dependent variable (PPR) is expected to depend on its values at previous time points since many of the causes of differences in adherence (some measurable and some unmeasurable) for an individual patients are unlikely to change between years; therefore, the lagged dependent variable PPR_{-1} needed to be included in the model.
3) In the panel data for the study, the variables were measured over the same time period (a year) hence the causality between exacerbation and adherence cannot be determined. To allow the partial evaluation of the effect of a previous exacerbation on adherence, the variable for exacerbation occurrence in the previous year was included (exacerbation occurrence lagged by 1 year).
4) There are many time independent effects (fixed effects) that could not be included in the model. These effects will be captured in the error term (λ), but may be correlated with the explanatory variables such as the clinical outcome variable.
5) The PPR data is known not to have a normal distribution due to the censoring at 100% for 28.2% of the adherence results, therefore a method that does not require a normal distribution must be used.

System generalised method of moments (system GMM) is a method used to estimate the parameters in panel data statistical models that can meet the requirements described above. It is an appropriate estimator to use for fixed effects models and can be used with characteristics of the data required for this study; including a mix of lagged dependent variables, endogenous and predetermined regressors as well as strictly exogenous regressors. [217]

The GMM estimator has been extensively studied and applied in numerous studies. [218-220] In this study, the GMM estimator was implemented using Roodman's xtabond2 algorithm [217] which is an add-on to the STATA software. [217]

To remove unobserved time invariant effects, described in problem 4, above, xtabond2 uses first differencing to provide consistent estimates. The first difference is the change between periods of time t−1 and t, ($\Delta Y_t = Y_t - Y_{t-1}$). However, when using differencing, time invariant explanatory variables (any variables that do not change over time) are also lost from the model. [216]

The error associated with endogeneity (correlation between adherence and the error term) cannot be removed using first differencing because this difference varies with time. Instead the GMM [221] uses lags in levels (i.e. values measured in previous years) of these endogenous variables as instruments making the endogenous variables become predetermined meaning that they are no longer correlated with the error term. [222] However, the use of these lagged levels can be poor instruments for first differences, especially, where values are based on previous values plus a random error. [223] The system GMM was instead developed, using two equations (the original and the equation transformed by first

differences), and makes the additional assumption that the first differences of instruments are uncorrelated with the fixed effects, so more instruments can be included, improving efficiency. [217]

8.3.4 Specification tests for the model

Stata provides 2 specification tests to test that the estimators are consistent and unbiased:

The Hansen J statistic [217] tests whether "the instruments as a group are exogenous with the error term" To improve the validity of the instruments, the number of instruments should be less than the number of individuals. [224] However, in this study, the number of patients included is extremely large, so will not be a problem in this study since, making this test unsuitable.

The Arellano- Bond test for first or second order serial correlation (autocorrelation), tests whether the lags of the dependent variable are endogenous. Within this study, we expect serial correlation within adherence since we expect for PPR to depend partly on its previous values, also making this test also unsuitable. The null hypothesis for the estimation is that" there is no autocorrelation." The null hypothesis should be rejected if $P<0.05$.

Therefore both specification tests are unsuitable; however, the power of the test is high due to the large number of data points (patients) included. Since the data set is very large, we can expect even small differences in adherence levels between subgroups of the variables to be statistically significant; therefore, care must be taken when interpreting the results of the model.

8.3.5 Variables to be included in the model

The characteristics of the explanatory variables (1, X_1, X_2, …X_K) and Y, determine how they needed to be included in the model, described below and presented in Table 8-2.

- Endogenous variables (Y) – those variables that are correlated with the future error term, must be instrumented using lags (previous values) of the variable in the GMM instrument set.
- Weakly (X) exogenous variables- only correlated with past error, but not future error, (predetermined since they have been recorded in the previous year) therefore included in the GMM instrument set with the endogenous variables. These variables are included in the estimation in their lagged form, so are also each included as an instrument in their lagged form.
- Strictly exogenous variables (X) -uncorrelated with the error term, so can be used as instruments for themselves.

Some of the variables that were measured in the data were time independent (variables that do not change over time such as gender or SES). These variables would be lost during the process of first differencing in the estimation of the model, where the differences between the values of a variable at different points in time are used. Therefore, these time independent variables were instead used to subgroup the cohort prior to analysis to try to observe the effect of these time independent variables on the estimated effects of each time variant patient characteristic on adherence. Therefore, the estimation was performed separately

for the time independent subgroups for gender, prescription exemption, socioeconomic status (by home address) and a comorbidity dummy variable.

Table 8-2. The variables to be included in each model within the four categories

Variables			**Analysis**									
Independent variable type	**coefficient**	Variables and Lagged variables	1	1a	1b	1c	1d	2	2a	2b	2c	2d
Endogenous variables	**γ**	Exacerbation occurrence primary care	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	γ	Exacerbation occurrence secondary care	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	$(\beta_0, \beta_1,\ldots,\beta_k)$	Exacerbation occurrence in previous year- primary care	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	$(\beta_0, \beta_1,\ldots,\beta_k)$	Exacerbation occurrence in previous year-secondary care	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Strictly exogenous	**$(\beta_0, \beta_1,\ldots,\beta_k)$**	Patient age	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	$(\beta_0, \beta_1,\ldots,\beta_k)$	Control by SABA use	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	$(\beta_0, \beta_1,\ldots,\beta_k)$	Year since entering study	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	$(\beta_0, \beta_1,\ldots,\beta_k)$	Treatment step	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	$(\beta_0, \beta_1,\ldots,\beta_k)$	Change in treatment step	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	$(\beta_0, \beta_1,\ldots,\beta_k)$	Smoking status- ever smoked	x	x	x	x	x	✓	✓	✓	✓	✓
	$(\beta_0, \beta_1,\ldots,\beta_k)$	ICS Drug substance	x	x	x	x	x	✓	✓	✓	✓	✓
	$(\beta_0, \beta_1,\ldots,\beta_k)$	Pregnancy indicator	x	x	x	x	x	✓	✓	✓	✓	✓
Weakly exogenous	**α**	PPR persistence (for past 2 years)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Time invariant	**n/a**	Gender	x	✓	x	x	x	x	✓	x	x	x
	n/a	Prescription exemption	x	x	✓	x	x	x	x	✓	x	x
	n/a	SES	x	x	x	✓	x	x	x	x	✓	x
	n/a	Comorbidity score	x	x	x	x	✓	x	x	x	x	✓

The syntax used for Stata is included in Appendix 20.

The first model that was estimated was quite basic, using only the main variables. The aim of this preliminary model was to enable a comparison of the consistency of the results against the more complex models to be made.

The second model included all of the variables considered to be important with some exclusions. The table is an outline of how each variable type in included in the xtabond2, Stata syntax (Table 8-2).

8.4 Results

The total study cohort included 1,181,023 individual years of data, from 292,735 patients, with 1 to 14 years of data for each patient. PPR could be calculated for 822,494 of these patient years for 215,202 patients. Of these 215,202 patients, 65,775 patients had fewer than 3 years of data recorded. Since over 2 years of data are required for the model, the cohort for the modelling estimation was reduced to 111,379 patients (680,623 patients' years).

The number of the patients able to be included in Analysis 1 and Analysis 2 were further reduced by some variables not being available for all patients (Appendix 21), meaning that the patient needed to be omitted from the analysis for any years where they had any missing data. This reduced the number of patients to 97456 (386488 observations) in analysis 1 was caused by missing data for the change in treatment step variable caused by the step change not being able to be calculated for the first year that patients are in the cohort. As expected, when the patients first year was excluded from the cohort, the mean PPR was slightly higher (70.22%) compared with the PPR for the full study cohort (67.56%). In the analysis 1 cohort, the patients with comorbidity and prescription co-payment exemption were slightly lower than the full cohort; however this could be due to the patients being a year older by the exclusion of their first year in the study data. All other variables were reasonably consistent between the cohorts.

In analysis 2, further patients were excluded due to missing smoking data, leaving 68782 patients (285973 observations). In addition to the small differences noted in the cohort for analysis 1, in the cohort for analysis 2, there were slightly higher

proportion of females included in the cohort for Analysis 2 (61%) than in the full study cohort (57%), which suggests that more females had a recorded smoking status than males. However, in analysis 2 the smoking status recorded was slightly lower for patients recorded as a smoker (50%) than for the full cohort (60%). All other variables were reasonably consistent between the cohorts.

The characteristics of the study cohort (for the patients with a measurable PPR) and the variables to be included in the model are presented in Table 8-3.

Table 8-3. Characteristics of the cohort included in the modelling for the patients where PPR could be measured

Variable name and definition		Variable type	Obs (N)	Mean	Min	Max
Adherence to ICS (PPR)		continuous	822494	67.56	0.46	100
The year that the variables are measured		continuous	822494	2005	1997	2010
Gender		dummy	822494	0.57	0	1
Socioeconomic status		categorical	817657	2.84	1	5
Comorbidities		dummy	822494	0.34	0	1
Co- payment exemption		dummy	822494	0.34	0	1
Patient Characteristics						
Age in years		categorical	822494	4	1	6
Smoking status (ever smoked)		dummy	578413	0.6	0	1
Drug substance	beclometasone	dummy	822494	0.63	0	1
	budesonide	dummy	822494	0.16	0	1
	ciclesonide	dummy	822494	0.002	0	1
	mometasone	dummy	822494	0.002	0	1
	fluticasone	dummy	822494	0.28	0	1
Pregnancy		dummy	822494	0.01	0	1
Secondary care exacerbation		dummy	822494	0.01	0	1
Primary care exacerbation		dummy	822494	0.2	0	1
Treatment step (set as 1-4 representing 2-5)		categorical	822949	1.83	1	4
Change in step from previous year		continuous	788248	0.04	-3	3
Greater than 10 doses of SABA per day		dummy	822949	0.05	0	1
Years in study		continuous	822949	6.58	1	14

The explanatory variables are described within four categories: patient characteristics, persistence, severity and asthma exacerbations. The estimation

results for each analysis in turn are presented in the following sections alongside the t-statistics (ratio of estimate to standard error) and P values.

8.4.1 Analysis 1 and 2

The two estimation results for the size of the effect of each variable included on adherence are presented in Table 8-4: for all patients for analysis 1 and 2.

Table 8-4. Estimation results for Analysis 1 and 2

	Analysis 1			**Analysis 2**		
Patient count *N*	97456			68782		
	Estimate	t-stat	P>t	Estimate	T-stat	P>t
Intercept	24.79	64.70	<0.0001	24.32	54.67	<0.0001
Persistence						
PPR_{-1}	0.51	141.87	<0.0001	0.50	118.73	<0.0001
PPR_{-2}	0.10	35.12	<0.0001	0.10	29.93	<0.0001
Patient Characteristics						
Age in years	0.11	33.77	<0.0001	0.11	28.05	<0.0001
Years in study	0.26	20.52	<0.0001	0.25	17.39	<0.0001
Poor control	5.63	23.57	<0.0001	5.21	19.12	<0.0001
Pregnant				0.51	1.08	0.28
Budesonide				1.94	11.91	<0.0001
Ciclesonide				7.60	6.89	<0.0001
Mometasone				1.12	1.02	0.31
Fluticasone				-2.00	-10.18	<0.0001
Smoking status				0.75	7.52	<0.0001
Severity						
Treatment step 3	-1.14	-7.08	<0.0001	-0.64	-4.11	<0.0001
Treatment step 4	-1.80	-6.61	<0.0001	-1.98	-7.83	<0.0001
Treatment step 5	-4.73	-8.03	<0.0001	-3.32	-4.87	<0.0001
Annual change in step	2.61	31.38	<0.0001	2.49	25.76	<0.0001
Exacerbations						
Primary care	-3.62	-2.28	0.02	0.63	0.36	0.72
Previous year primary care	1.27	7.16	<0.0001	0.87	4.39	<0.0001
Secondary care	-4.66	-0.82	0.41	-3.26	-0.57	0.57
Previous year secondary care	1.66	2.73	0.01	1.45	2.35	0.02

***Persistence*:** The estimates for the coefficients of lagged *adherence* (PPR_{-1} is current *PPR* lagged one year, and PPR_{-2} lagged by two years) are positive and statistically significant, where the previous year (Analysis 1: +0.51; t=141.87) (Analysis 2: +0.50;

t=118.73) shows a greater influence than the year before (Analysis 1: +0.10; t=35.12) (Analysis 2: +0.10; t=29.93).

***Characteristics*:** Adherence increases with patient age (Analysis 1: +0.11/year; t=33.77) (Analysis 2: +0.11/year; t=28.05) and also trends positively the longer the patient remains in the study (Analysis 1: years in study: +0.26/year; t=20.52) (Analysis 2: years in study: +0.25/year; t=17.39). Poor asthma control (where a 1 indicates high use of SABA, associated with poor control) had an increasing effect on adherence (Analysis 1: +5.63; t=23.57) (Analysis 2: +5.21; t=19.12).

Patients who have ever smoked (+0.75; t=7.52), included in analysis 2, had a slightly increased adherence compared with patients who had not.

In analysis 2, an increase in adherence was seen when the corticosteroid prescribed was ciclesonide (+7.60; t=6.89) and budesonide (+1.94; t=11.90). Patients prescribed fluticasone has a slightly lower adherence measured (-2.00; t=-10.18).

Severity: Adherence was found to worsen when patients were treated at higher treatment steps (BTS/SIGN guidelines) (when compared with the mean adherence if those patients treated within step 2). When a patients treatment step change from the previous year, the patient adherence was observed to increases by +2.61 per step increase (t=31.38) in analysis 1 and by +2.49 times per step increase (t=25.76) in analysis 2, however, conversely, a patient with an improvement in their asthma treatment step from the previous year is, expected to worsen in adherence also by 2.61 and -2.49 per step respectively.

***Exacerbations*:** The occurrence of an exacerbation within the same year, measured within primary care, had a negative effect on adherence (Analysis 1: -3.62; t=-2.28) (not found to be significant in analysis 2). Patients who experienced one or more exacerbations in the previous year, which required treatment within primary care, were found to have an increased adherence (Analysis 1: 1.27, t=7.16) (Analysis2: 0.87, t=4.39). The occurrence of a secondary care exacerbation within the same year was not found to have a significant effect on adherence. The effect of an exacerbation in the previous year, requiring treatment within secondary care was an increasing effect on adherence (Analysis 1: +1.66 t=2.73) (Analysis 2: +1.45; t=2.35), which was greater than those patients who experience a primary care exacerbation during the previous year. In the analysis, the variables that were not found to have a significant effect on PPR included pregnancy status and mometasone prescription dummy.

8.4.2 Analysis 1a and 2a by gender

Two sets of estimation results for the size of the effect of each variable included on adherence are presented by gender in Table 8-5, and any gender differences observed are discussed below.

Table 8-5. Estimation results for Analysis 1a and 2a subgrouped by gender

	Males 1a			Females 1a			Males 2a			Females 2a		
Patient count *N*	42740			54716			29839			38943		
	Est.	t-stat	P>t	Est.	t-stat	P>t	Est.	T-stat	P>t	Est.	T-stat	P>t
Intercept	25.58	41.26	<0.0001	23.92	47.81	<0.0001	25.50	35.14	<0.0001	23.11	38.23	<0.0001
Persistence												
PPR_{-1}	0.50	88.75	<0.0001	0.51	109.94	<0.0001	0.49	74.02	<0.0001	0.50	91.94	<0.0001
PPR_{-2}	0.10	21.87	<0.0001	0.10	26.72	<0.0001	0.10	17.91	<0.0001	0.11	23.14	<0.0001
Patient Characteristics												
Age in years	0.11	25.31	<0.0001	0.12	26.91	<0.0001	0.11	19.82	<0.0001	0.12	21.17	<0.0001
Years in study	0.25	12.65	<0.0001	0.27	16.14	<0.0001	0.24	10.40	<0.0001	0.27	14.51	<0.0001
Poor control	5.23	19.78	<0.0001	5.51	15.52	<0.0001	5.13	13.60	<0.0001	5.05	10.26	<0.0001
Pregnant										0.59	1.15	0.25
Budesonide							1.82	7.51	<0.0001	1.93	8.24	<0.0001
Cclesonide							8.07	3.64	<0.0001	7.11	5.69	<0.0001
Mometasone							0.76	0.43	0.67	1.12	0.79	0.43
Fluticasone							-2.22	-8.10	<0.0001	-2.00	-6.95	<0.0001
Smoking status							0.91	5.90	<0.0001	0.63	4.44	<0.0001
Severity												
Treatment step 3	-1.38	-8.01	<0.0001	-1.22	-5.37	<0.0001	-0.58	-2.59	0.01	-0.72	-3.21	<0.0001
Treatment step 4	-2.11	-9.04	<0.0001	-2.12	-5.37	<0.0001	-1.85	-5.93	<0.0001	-2.26	-5.41	<0.0001
Treatment step 5	-2.69	-3.45	<0.0001	-5.25	-7.19	<0.0001	-1.78	-1.80	0.07	-4.18	-4.12	<0.0001
Annual change in step	2.23	17.19	<0.0001	2.80	25.67	<0.0001	2.13	14.20	<0.0001	2.66	21.14	<0.0001
Exacerbations												
Primary care	-1.30	-1.01	0.31	-1.77	-0.89	0.38	1.23	0.55	0.58	1.42	0.51	0.61
Previous year primary care	1.24	5.22	<0.0001	1.05	4.76	<0.0001	0.90	2.97	<0.0001	0.77	3.07	<0.0001
Secondary care	-11.93	-1.86	0.06	3.10	0.53	0.59	-6.39	-0.84	0.40	6.27	1.77	0.08
Previous year secondary care	2.93	3.01	<0.0001	1.12	1.48	0.14	2.34	2.33	0.02	0.99	1.09	0.28

When sub grouped by gender, by looking at the intercept alone, PPR is lower in female patients, but this is altered by the estimated effects of each patient variable on the PPR. In both analysis 1 and 2, no significant result was recorded for an exacerbation that occurred within either primary or secondary care, within the same year as adherence was measured, for both genders and an exacerbation that occurred in the previous year, which required secondary care treatment in females, pregnancy status and mometasone prescription dummy.

***Characteristics*:** For patients who had smoked, the female patients had a smaller increase in PPR (0.63; t=4.44) than the male patients (0.91; t=5.90).

In analysis 2, a larger increase in adherence was seen when the corticosteroid prescribed was ciclesonide in males (+8.07; t=3.64), and budesonide in females (+1.93; t=11.90), when compared with those patients prescribed beclometasone. Patients prescribed fluticasone had a slightly lower adherence in males (-2.22; t=-8.10). In analysis 1, females with poor control in the same year are associated with larger increase in adherence of +5.51 (t=15.52) compared with the increase for males of +5.23 (t=19.78).

Severity: A larger decreasing effect of treatment step on PPR was observed in females than in males. The effect of a step change from the previous year was slightly more pronounced in females than males where a decrease in PPR was observed alongside a decrease in treatment step. A larger increase in PPR was associated with females with an increase in treatment step (Analysis 1: 2.80, t=25.67) (Analysis 2: 2.66, t=21.14) compared with males (Analysis 1: 2.23, t=17.19) (Analysis 2: 2.13, t=14.20).

***Exacerbations*:** The effect of a primary care exacerbation in the previous year was greater in males (Analysis 1: +1.24; t=5.22) (Analysis 2: 0.90; t=2.97) than females (Analysis 1: +1.05; t=4.76) (Analysis 2: 0.77; t=3.07.

8.4.3 Analysis 1b and 2b by prescription exemption

Two sets of estimation results for the size of the effect of each variable on adherence are presented by patients with and without a prescription exemption

status (Table 8-6) and any differences observed between prescription exemption statuses are described below.

Table 8-6. Estimation results for Analysis 1b and 2b subgrouped by exemption

	Exempt 1b			**Not exempt 1b**			**Exempt 2b**			**Not exempt 2b**		
Patient count *N*	34746			62710			24149			44633		
	Est.	T-stat	P>t	Est.	T-stat	P>t	Est.	T-stat	P>t	Est.	T-stat	P>t
Intercept	23.89	35.81	<0.0001	25.60	52.55	<0.0001	23.74	30.14	<0.0001	24.86	43.89	<0.0001
Persistence												
PPR_{-1}	0.50	79.71	<0.0001	0.50	116.54	<0.0001	0.49	66.64	<0.0001	0.50	98.28	<0.0001
PPR_{-2}	0.10	19.65	<0.0001	0.10	28.06	<0.0001	0.10	17.02	<0.0001	0.10	24.00	<0.0001
Patient Characteristics												
Age in years	0.12	28.12	<0.0001	0.11	18.50	<0.0001	0.12	24.03	<0.0001	0.10	15.41	<0.0001
Years in study	0.29	13.72	<0.0001	0.24	14.96	<0.0001	0.30	12.30	<0.0001	0.24	12.72	<0.0001
Poor control	5.43	15.58	<0.0001	5.36	17.76	<0.0001	5.56	13.34	<0.0001	4.67	13.02	<0.0001
Pregnant							-0.57	-0.31	0.75	0.45	0.92	0.36
Budesonide							1.40	5.67	<0.0001	2.00	9.11	<0.0001
Ciclesonide							8.48	3.37	<0.0001	6.77	5.66	<0.0001
Mometasone							1.87	0.92	0.36	0.21	0.16	0.88
Fluticasone							-2.12	-7.82	<0.0001	-2.30	-8.77	<0.0001
Smoking status							0.21	1.24	0.21	0.90	6.98	<0.0001
Severity												
Treatment step 3	-1.13	-4.80	<0.0001	-1.51	-7.52	<0.0001	-0.11	-0.43	0.67	-1.05	-5.50	<0.0001
Treatment step 4	-2.56	-7.23	<0.0001	-2.14	-6.14	<0.0001	-1.96	-5.93	<0.0001	-2.49	-7.76	<0.0001
Treatment step 5	-3.16	-4.08	<0.0001	-5.24	-7.13	<0.0001	-1.85	-2.21	0.03	-4.52	-5.22	<0.0001
Annual change in step	2.70	19.81	<0.0001	2.54	23.89	<0.0001	2.55	15.61	<0.0001	2.41	19.66	<0.0001
Exacerbations												
Primary care	1.24	0.63	0.53	-2.50	-1.33	0.18	2.04	0.98	0.33	2.88	1.40	0.16
Previous year primary care	0.96	3.69	<0.0001	1.16	5.25	<0.0001	0.67	2.25	0.02	0.77	3.12	<0.0001
Secondary care	5.65	0.71	0.48	-1.49	-0.24	0.81	7.18	0.92	0.36	1.74	0.27	0.79
Previous year secondary care	1.84	1.71	0.09	1.33	1.75	0.08	1.26	1.03	0.30	0.94	1.24	0.21

When sub grouped by exemption, by looking at the intercept alone, PPR is lower in exempt patients, but this is altered by the estimated effects of each patient variable on the PPR. Some variables were not found to have any statistically significant effect on adherence including the occurrence of a primary care exacerbation in the same year as PPR was measured, or for secondary care in the same or the previous year that PPR was measured.

In analysis 2, in addition, no significant effects could be reported for pregnancy status, mometasone prescription dummy. For the exempt patients, step 3 treatment and smoking status were also not significant. All other results were significant, where some showed differences in effects between the exempt and non-exempt subgroups of patients:

Characteristics: Poor control was found to have a larger positive effect on adherence in patients who were exempt (Analysis 1: +5.43; t=5.58) (Analysis 2: +5.56; t=13.34) compared with non-exempt (Analysis 1: +5.36; t=17.76) (Analysis 2: +4.67; t=13.02).

Adherence was found to worsen as the non-exempt patients were treated at higher steps in the BTS/SIGN guidelines, with the largest negative effect observed in non-exempt patients, treated at step 5 (Analysis 1: -5.24; t=-7.13) (Analysis 2: -4.52; t=-5.22). However, the effect of a step change from the previous year was slightly more pronounced in exempt than in non-exempt patients where a decrease in PPR was observed alongside a decrease in treatment step from the previous year.

In analysis 2, increased adherence was seen when the corticosteroid prescribed was ciclesonide; with a larger effect observed in exempt patients (+8.48; t=3.37). Increased adherence was also seen when the patient was prescribed budesonide with a larger increasing effect on adherence observed in the non-exempt patients. When fluticasone was prescribed a negative effect on adherence was observed, with a slightly lower PPR found in non-exempt patients (-2.30; t=-8.77).

***Exacerbations*:** Patients exempt from payment who experienced one or more exacerbations in the previous year treated within primary care, were found to have a slightly lower adherence (Analysis 1: +0.69; t=3.69) (Analysis 2: +0.67; t=2.25) than if they were not exempt (Analysis 1: +1.16; t=5.25) (Analysis 2: +0.77; t=3.12).

8.4.4 Analysis 1c and 2c by socioeconomic status

Five sets of estimation results for the size of the effect of each variable on adherence by socioeconomic status (groups 1 to 5), by the patient's home address (Table 8-7). Any differences observed by socioeconomic status are described below.

Table 8-7. Estimation results for Analysis 1c subgrouped by socioeconomic status

	1 (Least deprived)			2			3			4			5 (Most deprived)		
Patient count *N*	21116			21918			18981			19338			15565		
	Est.	t-stat	P>t	Est.	t-stat	P>t	Est.	t-stat	P>t	Est.	t-stat	P>t	Est.	t-stat	P>t
Intercept	23.89	29.17	<0.0001	24.72	31.40	<0.0001	24.35	27.28	<0.0001	24.49	28.09	<0.0001	26.99	27.80	<0.0001
Persistence															
PPR_{-1}	0.50	64.35	<0.0001	0.50	66.15	<0.0001	0.50	60.92	<0.0001	0.51	62.69	<0.0001	0.50	55.74	<0.0001
PPR_{-2}	0.11	17.84	<0.0001	0.10	15.61	<0.0001	0.11	15.61	<0.0001	0.10	14.81	<0.0001	0.08	11.18	<0.0001
Patient characteristic															
Age in years	0.10	14.42	<0.0001	0.12	17.31	<0.0001	0.11	15.46	<0.0001	0.12	16.10	<0.0001	0.12	14.21	<0.0001
Years in study	0.27	10.15	<0.0001	0.21	8.16	<0.0001	0.28	9.59	<0.0001	0.29	10.03	<0.0001	0.31	9.35	<0.0001
Poor control	5.17	10.37	<0.0001	4.62	9.08	<0.0001	5.02	11.43	<0.0001	5.70	12.48	<0.0001	5.26	11.89	<0.0001
Severity															
Treatment step 3	-1.32	-4.57	<0.0001	-1.21	-4.06	<0.0001	-1.13	-3.54	<0.0001	-1.41	-4.35	<0.0001	-2.77	-7.50	<0.0001
Treatment step 4	-2.50	-5.71	<0.0001	-2.46	-5.09	<0.0001	-2.39	-5.22	<0.0001	-2.19	-4.24	<0.0001	-3.36	-6.41	<0.0001
Treatment step 5	-3.14	-2.86	<0.0001	-3.07	-2.94	<0.0001	-4.03	-3.51	<0.0001	-4.21	-3.40	<0.0001	-5.14	-3.90	<0.0001
Annual change in step	2.62	15.01	<0.0001	2.36	13.53	<0.0001	2.81	14.68	<0.0001	2.43	12.80	<0.0001	2.65	12.68	<0.0001
Exacerbation															
primary care	1.44	0.56	0.57	1.80	0.68	0.50	1.43	0.57	0.57	-2.65	-0.94	0.35	2.60	0.89	0.37
Previous year primary care	1.03	3.01	<0.0001	1.10	3.41	<0.0001	0.94	2.65	0.01	1.05	2.93	<0.0001	0.25	0.63	0.53
Secondary care	6.53	1.07	0.28	-1.13	-0.36	0.72	-6.34	-0.92	0.36	8.12	1.24	0.21	-12.18	-1.66	0.10
Previous year secondary care	3.53	2.62	0.01	1.69	1.42	0.16	2.58	1.69	0.09	0.68	0.51	0.61	0.13	0.10	0.92

Table 8-8. Estimation results for Analysis 2c subgrouped by socioeconomic status

	1 (Least deprived)			2			3			4			5 (Most deprived)		
Patient count *N*	15772			15393			13103			13334			10801		
	Est.	t-stat	P>t	Est.	t-stat	P>t	Est.	t-stat	P>t	Est.	t-stat	P>t	Est.	t-stat	P>t
Intercept	23.75	25.63	<0.0001	23.98	26.13	<0.0001	24.60	22.97	<0.0001	24.41	23.72	<0.0001	26.92	23.31	<0.0001
Persistence															
PPR_{-1}	0.49	54.90	<0.0001	0.50	56.90	<0.0001	0.49	50.21	<0.0001	0.51	52.15	<0.0001	0.49	44.76	<0.0001
PPR_{-2}	0.11	15.34	<0.0001	0.10	13.29	<0.0001	0.10	12.30	<0.0001	0.10	12.62	<0.0001	0.08	9.65	<0.0001
Patient characteristics															
Age in years	0.10	13.06	<0.0001	0.12	14.71	<0.0001	0.11	12.72	<0.0001	0.12	13.32	<0.0001	0.11	11.43	<0.0001
Years in study	0.25	8.09	<0.0001	0.21	7.02	<0.0001	0.30	8.66	<0.0001	0.30	9.01	<0.0001	0.31	7.83	<0.0001
Poor control	4.96	8.37	<0.0001	4.76	8.20	<0.0001	4.68	9.09	<0.0001	5.22	10.71	<0.0001	4.85	9.53	<0.0001
pregnant	1.25	1.29	0.20	-0.60	-0.58	0.57	1.11	1.10	0.27	0.94	0.84	0.40	-0.12	-0.10	0.92
budesonide_y_n	2.34	7.39	<0.0001	1.63	4.91	<0.0001	1.70	4.82	<0.0001	1.55	4.46	<0.0001	1.06	2.51	0.01
ciclesonide_y_n	7.30	3.31	<0.0001	6.43	2.88	<0.0001	7.15	2.35	0.02	6.84	2.31	0.02	7.88	4.20	<0.0001
mometasone_y_n	-1.77	-0.81	0.42	2.24	1.12	0.26	2.37	0.87	0.38	1.71	0.61	0.54	-1.01	-0.36	0.72
fluticasone_y_n	-2.25	-6.29	<0.0001	-1.84	-5.07	<0.0001	-2.01	-5.59	<0.0001	-2.81	-7.04	<0.0001	-3.15	-7.15	<0.0001
Smoking status	0.79	3.89	<0.0001	0.83	4.03	<0.0001	0.55	2.39	0.02	0.26	1.11	0.27	0.67	2.38	0.02
Severity															
Treatment step 3	-0.51	-1.69	0.09	-0.47	-1.52	0.13	-0.70	-1.97	0.05	-0.43	-1.27	0.21	-1.67	-4.16	<0.0001
Treatment step 4	-2.32	-5.75	<0.0001	-2.02	-4.53	<0.0001	-2.72	-5.70	<0.0001	-1.98	-4.33	<0.0001	-2.65	-5.01	<0.0001
Treatment step 5	-2.93	-2.28	0.02	-1.81	-1.51	0.13	-3.78	-2.82	0.01	-3.37	-2.41	0.02	-2.76	-1.88	0.06
Annual change in step	2.55	12.94	<0.0001	2.15	10.56	<0.0001	2.50	10.98	<0.0001	2.47	11.39	<0.0001	2.54	10.08	<0.0001
Exacerbations															
primary care	2.85	1.08	0.28	2.65	0.96	0.34	5.39	1.89	0.06	1.12	0.40	0.69	6.78	2.08	0.04
Previous year primary care	0.98	2.72	0.01	1.09	2.99	<0.0001	0.36	0.87	0.38	0.67	1.68	0.09	-0.22	-0.48	0.63
Secondary care	8.41	1.42	0.16	-0.72	-0.26	0.79	-4.49	-0.72	0.47	12.41	1.92	0.06	-9.83	-1.32	0.19
Previous year secondary care	2.93	2.19	0.03	1.83	1.52	0.13	1.97	1.27	0.21	1.28	0.93	0.35	-0.18	-0.14	0.89

When sub grouped by socioeconomic status, by looking at the intercept alone, PPR is lower in the least deprived patients, but this is altered by the estimated effects of each patient variable on the PPR. Some variables were not found to have a statistically significant effect on adherence or had very few significant results across each socioeconomic status, these included the effect of a primary or secondary care exacerbation occurring in the same year as PPR was measured, the effect of secondary care exacerbation in the previous year that PPR was measured and in analysis 2, additionally, pregnancy, mometasone prescribing, patients treated at step 5 and the occurrence of an exacerbation within the previous year for a primary care exacerbation. Most other results were significant, where some showed differences in effects between the socioeconomic status subgroups of patients:

***Characteristics*:** Poor control was found to have a slightly more positive effect on patients in the most deprived group (5.26; t=11.89) than those patients in the least deprived group (5.17; t=10.37) in analysis 1, but little difference was observed in analysis 2. The trend of an increasingly negative effect on PPR with increasing treatment step was observed across socioeconomic status groups, where the largest negative effect was seen in the most deprived patients (step 5, most deprived -5.14, t=-3.90) when compared with the other socioeconomic groups (step 5, least deprived -3.14, t=-2.86) in analysis 1, but no consistent trend was observed in analysis 2.

In analysis 2, increased adherence was seen when the corticosteroid prescribed was budesonide; with a larger effect observed in the least deprived patients (+2.34; t=7.39). When fluticasone was prescribed a negative effect on adherence was

observed, with the lowest PPR found in most deprived patients (-3.15; t=-7.15). Increased adherence was noted when ciclesonide was prescribed, with a larger increase in adherence seen in the most deprived patients (+7.88; t=4.20).

A slightly larger increasing effect on adherence was found in patients who smoked within the least deprived subgroup compared with the most deprived group.

***Exacerbations*:** Where significant results for the effect of experiencing one or more exacerbations in the previous year were recorded, no consistent trend could be observed by socioeconomic status.

8.4.5 Analysis 1d and 2d by comorbidity dummy

Two sets of estimation results for the size of the effect of each variable by differences observed between patients with and without comorbidities are described below (Table 8-9).

Table 8-9. Estimation results for Analysis 1d and 2d subgrouped by comorbidity status

	No comorbidities 1d			1 or more comorbidities 1d			No comorbidities 2d			At least 1 comorbidity 2d		
Patient count *N*	64383			33073			45327			23455		
	Est.	T-stat	P>t	Est.	T-stat	P>t	Est.	T-stat	P>t	Est.	T-stat	P>t
Intercept	24.29	51.60	<0.0001	25.46	37.12	<0.0001	23.94	43.24	<0.0001	24.94	30.49	<0.0001
Persistence												
PPR_{-1}	0.51	115.96	<0.0001	0.50	78.41	<0.0001	0.50	96.60	<0.0001	0.49	64.72	<0.0001
PPR_{-2}	0.10	28.34	<0.0001	0.10	19.39	<0.0001	0.10	24.06	<0.0001	0.10	16.09	<0.0001
Patient Characteristics												
Age in years	0.11	28.92	<0.0001	0.10	17.54	<0.0001	0.11	24.84	<0.0001	0.09	14.30	<0.0001
Years in study	0.26	16.08	<0.0001	0.25	12.13	<0.0001	0.26	13.74	<0.0001	0.25	10.73	<0.0001
Poor control	5.29	19.77	<0.0001	4.44	12.24	<0.0001	5.14	16.67	<0.0001	4.09	11.23	<0.0001
pregnant							0.80	1.47	0.14	-0.82	-0.87	0.39
budesonide_y_n							1.84	9.55	<0.0001	1.49	5.62	<0.0001
ciclesonide_y_n							7.02	4.79	<0.0001	7.02	4.57	<0.0001
mometasone_y_n							0.42	0.30	0.76	1.29	0.72	0.47
fluticasone_y_n							-2.37	-11.65	<0.0001	-2.46	-7.33	<0.0001
Smoking status							0.69	5.69	<0.0001	0.68	3.91	<0.0001
Severity												
Treatment step 3	-1.64	-9.51	<0.0001	-1.41	-5.14	<0.0001	-0.65	-3.49	<0.0001	-0.93	-3.74	<0.0001
Treatment step 4	-2.82	-10.36	<0.0001	-2.48	-5.43	<0.0001	-2.39	-9.28	<0.0001	-2.59	-7.04	<0.0001
Treatment step 5	-4.65	-5.63	<0.0001	-2.72	-3.31	<0.0001	-3.69	-3.87	<0.0001	-1.06	-1.21	0.23
Annual change in step	2.70	25.71	<0.0001	2.36	17.18	<0.0001	2.60	21.19	<0.0001	2.30	14.03	<0.0001
Exacerbations												
primary care	0.60	0.39	0.70	3.40	1.36	0.17	1.82	1.12	0.26	8.53	4.02	<0.0001
Previous year primary care	0.92	4.75	<0.0001	0.81	2.57	0.01	0.71	3.29	<0.0001	0.35	1.31	0.19
Secondary care	6.24	1.04	0.30	-11.41	-1.62	0.11	7.15	1.14	0.25	-12.30	-1.84	0.07
Previous year secondary care	2.14	2.69	0.01	1.48	1.44	0.15	1.95	2.36	0.02	1.79	1.71	0.09

When sub grouped by comorbidity, by looking at the intercept alone, PPR is lower in patients with no additional comorbidities, but this is altered by the estimated effects of each patient variable on the PPR.

Some variables were not found to have a statistically significant effect on adherence nor had very many significant results across socioeconomic status, these included, for both models, the occurrence of a primary care exacerbation measured within the same year as adherence, and the effect of an exacerbation within the previous

year in patients with over 1 comorbidity. In analysis 2, additionally the following results were not significant; pregnancy status and mometasone prescription. Other variables only had one significant result across the two groups so could not be compared. Of the results that were significant, some showed differences in effects between the comorbidity subgroups of patients:

***Characteristics*:** Poor control was found to have a slightly more positive effect on patients with no comorbidities (Analysis 1: 5.29; t=19.77) (Analysis 2: 5.14; t=16.67) than those patients with >1 comorbidity (Analysis 1: 4.44; t=12.24) (Analysis 2: 4.09; t=11.23). In general a larger negative effect with higher treatment step was observed in both groups, but was more pronounced in the patients with no additional comorbidities. The effect of a step change from the previous year was slightly more pronounced in patients who had no additional comorbidities, where an increase in PPR was observed alongside an increase in treatment step (Analysis 1; 2.70; t=25.71). (Analysis 2; 2.60; t=21.19).

In analysis 2, increased adherence was observed when the corticosteroid prescribed was budesonide; with a larger effect observed in the patients with no additional comorbidities (+1.84; t=9.55). When fluticasone was prescribed a negative effect on adherence was observed, with the lowest PPR found in the patients with at least 1 comorbidity (-2.46; t=-7.33).

Exacerbation: In analysis 1, patients who experienced one or more exacerbations in the previous year treated within primary care, were found to have a greater increasing effect on adherence if they had only one comorbidity (+0.92; t=4.75) than if they had over 1 comorbidity (+0.81; t=2.57).

8.4.6 Specification tests for the model

The Hansen test has the null hypothesis "the instruments as a group are exogenous", therefore, the result of p=0 suggests that the instruments are endogenous and may be weak. However, the Stata output recorded that the instruments were robust, but the test was weakened by many instruments. However, as discussed in Section 8.3.4., to improve the validity of the instruments, the number of instruments should be less than the number of individuals. [224] In this study the number of individual (patients) was extremely high increasing the validity of the instruments. Therefore we can be confident that the instruments specified were robust.

The Arellano-Bond test for serial correlation, has the null hypothesis" there is no autocorrelation". Since P>0.05 for all tests except for the subgroup for prescription exempt patients, the null hypothesis cannot be rejected, and therefore autocorrelation was present (Table 8-10). In this study we expected serial correlation to be present, hence we included PPR in the previous year as an independent variable.

Table 8-10. Specification test results

	Analysis 1		Analysis 2	
Sub group	**AR2**	**Hansen***	**AR2**	**Hansen***
All	0.794	**<0.0001**	0.917	**<0.0001**
Males	0.844	**<0.0001**	0.930	**<0.0001**
Females	0.424	**<0.0001**	0.715	**<0.0001**
exempt	0.723	**<0.0001**	0.835	**<0.0001**
Non exempt	0.867	**<0.0001**	0.998	**<0.0001**
Deprivation-5 (Most deprived)	0.778	**<0.0001**	0.859	**<0.0001**
Deprivation-4	0.206	**<0.0001**	0.217	**<0.0001**
Deprivation-3	0.386	**<0.0001**	0.543	**<0.0001**
Deprivation-2	0.365	**<0.0001**	0.588	**<0.0001**
Deprivation-1	0.876	**<0.0001**	0.869	**<0.0001**
1 comorbidity	0.346	**<0.0001**	0.388	**<0.0001**
> 1 comorbidity	0.144	**<0.0001**	0.210	**<0.0001**

***For all analysis, the Hansen test noted "Robust, but weakened by many instruments"**

8.4.7 Summary of results

A variety of the risk factors were found for lower adherence from both models (Table 8-11. Summary of results).

Table 8-11. Summary of results

	variable name	subgroup	Analysis 1			Analysis 2		
			Lower PPR associated with…	Increased adherence with…	Decreased adherence with…	Lower PPR associated with…	Increased adherence with…	Decreased adherence with…
Time dependent variables	**Adherence persistence**	PPR-previous year	Low previous PPR			Low previous PPR		
		PPR- 2 years previous	Low previous PPR			Low previous PPR		
	Age in years		Younger age			Younger age		
	Years in study		Fewer years in study			Fewer years in study		
	Poor control		Good control			Good control		
	Pregnancy	n/a	n/a			Not significant		
	Drug substance	none	n/a			Fluticasone		
	Smoking	Ever smoked?	n/a			Non-smoker,		
	Asthma severity		Higher step			Higher step		
	Change in step		Decrease in step			Decrease in step		
	Primary care exacerbation	Same year	Exacerbation			No significant		
		Previous year	No exacerbation			No exacerbation		
	Secondary care exacerbation	Same year	Not significant			Not significant		
		Previous year	No exacerbation			No exacerbation		
Time independent variables	**Gender**	Male	Female	Primary care exacerbation (previous year)	Step 3	Female	Primary care exacerbation (previous year), smoker, ciclesonide prescription	Fluticasone prescription, poor control
		Female		Poor control and increase in treatment step	Treatment step 5.		Budesonide prescription and increase in treatment step	Treatment steps higher than 2
	Socioeconomic status	Most deprived	Least deprived	Poor control	Treatment steps higher than 2	Least deprived	Ciclesonide prescription	Fluticasone prescription, step 3/ 4
		Least deprived		None	None		Budesonide prescriptions, smoking, step 5, poor control	None
	Comorbidities	No comorbidity	No comorbidities	Primary care exacerbation (previous year), poor control, increase in step	Treatment steps higher than 2 and 3	No comorbidities	Budesonide prescription, poor control, increase in step	Step 5
		At least 1 comorbidity		None	None		Primary care exacerbation (same year)-large positive effect.	Fluticasone prescription, and at treatment steps 3 or 4
	Prescription exemption	Exempt	Exempt	Increase in step, poor control	Step 4	Exempt	Ciclesonide prescription, poor control, increase in step	None
		Non exempt		Primary care exacerbation (previous year)	Step 3 and 5		Primary care exacerbation (previous year), budesonide prescription, smoker	Treatment steps higher than 2 and fluticasone.

8.5 Discussion

The aim of this chapter was to model asthma patient's adherence to ICS over time, adjusting for both time dependent and time independent variables. Time dependent variables were included in the model, and the time independent variables in the table were used to subgroup the patients prior to estimation since they could not be included in the selected model.

The estimated effects of the time dependent variables from the models are discussed below, and then the differences in the estimates between each time independent subgroup are then discussed to assess the effect of each subgroup on the estimate.

8.5.1 The effect of time dependent patient variables on adherence

8.5.1.1 Persistence in PPR

The patient's previous adherence was estimated to have a significant reinforcing effect on future adherence (0.50% in the previous year, and 0.10% for 2 years previous for every percentage increase in adherence). This effect represents the many unmeasurable patient variables that effect adherence, especially those that do not change or do not significantly change between years. This is expected since many of the measured patient characteristics that may affect adherence will not change significantly over time.

8.5.1.2 Age

As expected, the effect of an increase in age was an increase in PPR by 'age x 0.12', however, in the analysis in Chapter 6 it was observed that the relationship between

PPR and age was not linear so this result should be interpreted as an average increase in PPR between years.

8.5.1.3 Years in study

For each year that a patient remained in the study, the mean increase in adherence was estimated to be approximately 0.26% from the year before. This increase is not consistent with other studies and the general belief that, adherence will decrease over time; however, previous studies only followed adherence for a short period of time using smaller intervals. [140 141]

8.5.1.4 Control by SABA use

Patients with poor control (high SABA use) were found to have a higher adherence than those patients with low SABA use. This is unexpected, but consistent with the findings in Chapter 6. As discussed in Chapter 6, using prescription records rather than actual measures of medicine taking for both variables, we cannot differentiate whether the relationship between poor control and high adherence is caused by patients being treated at a step where their asthma remains extremely uncontrolled despite adherence to their ICS; or because the characteristics of a patient that receives prescription for their SABA regularly may also make the patient more inclined to receive regular prescriptions for their ICS. However, we cannot know whether the patient has taken either drug as prescribed.

8.5.1.5 Pregnancy

The coefficients calculated for the effect of pregnancy on adherence were not found to be significant; this may be due to the variability of the patients within this subgroup. As discussed in Chapter 6, patients who were pregnant may choose to be

more adherent to prevent exacerbation of asthma symptoms, or alternatively may try to avoid any 'unnecessary' medicines. This effect may have differed by the severity of the patient's asthma and unmeasurable characteristics, explaining the variance in the results.

8.5.1.6 Drug substance

When compared with patients prescribed beclometasone, those patients taking ciclesonide had the highest adherence, followed by budesonide, then mometasone, where patients who were prescribed fluticasone had a lower mean PPR. This was consistent with the findings in Chapter 6, where the drug substance was also found to be linked to asthma severity, which is also related to adherence. A smaller increasing effect by treatment step was noted when drug substance was added to the model.

8.5.1.7 Smoking Status

Patients who smoked, or had smoked were found to have a higher adherence than those patients who had never smoked. The results were consistent between the 2 way and the modelling analysis, thought to be caused by the perceived risk of exacerbation leading to better adherence in smokers who would be expected to have experienced more symptoms of their asthma.

8.5.1.8 Treatment step

In the model, the opposite effect to that observed in the two-way analysis was recorded, where patients treated at a higher treatment step were associated with a lower adherence. This result may be caused by other variables in the model that were likely to be co-dependent with treatment step, such as control, treatment step

change or drug substance, which may have contributed to a large increase in adherence observed in the 2 way analysis, but, then reduced by the negative affect of each increasing step observed separately in the model. A smaller decreasing effect on the PPR with increasing treatment step was observed when drug substance was added to the model (Analysis 2). This may be related to the drug substances that were found to be more likely to be prescribed at each asthma severity step (Figure 6-5, page 193), where at step 5 fluticasone or beclomethasone were prescribed most often. In Analysis 1, the drug substance was not included in the model, so the effect of the drug substance prescribed on PPR was partially observed in the effect of the patient's asthma severity on PPR. In analysis 2 the effect of a step 5 exacerbation on PPR is not as low as in Analysis 1, since in analysis 2 fluticasone prescribing was included in the model separately and contributed separately to a decreasing effect on PPR.

A change in treatment step from the previous year was found to have a large positive effect on adherence when treatment step was increased, when compared with patients with no step change. This increase in step i.e. a new treatment plan being agreed with or arranged for the patient is likely to be either at the point where a patient is recognised to need to improve their asthma control, or following an exacerbation of asthma. However, the cause of the poor control may be low adherence to the prescribed medicines at the lower treatment step. Therefore, patients could be treated at higher steps (considered to have more severe asthma) because they are not adherent, so not receiving the benefit of their prescribed

medicines. At this point in their treatment asthma patients may improve adherence since they would perceive their medicines to be more important.

8.5.1.9 Exacerbation

As expected, the occurrence of an exacerbation within both primary and secondary care, when measured over the previous year to PPR, was associated with an increase in PPR. This is generally consistent with the findings in Chapter 7, for secondary care exacerbations, but in Chapter 7, primary care results were not consistent.

The effect of an exacerbation on adherence when measured over the same year was generally not statistically significant, apart from in the simple model for primary care where an exacerbation was associated with lower adherence. In this simple model drug substance prescribed and smoking status were not included, both of which were found to have an increasing effect on PPR in the second model.

8.5.2 The effect of time independent patient variables on adherence

8.5.2.1 Gender

When the patients were sub-grouped by gender prior to running the model, mean adherence was slightly higher for males than females but male patients had a larger response in increasing their adherence to an exacerbation of their asthma, smoking and ciclesonide prescribing. Male patients with the most severe asthma had a higher PPR than females at the same step, but females responded to an increase in treatment step by a greater increase in adherence.

These gender differences may be caused by differences in how women use health care, for example, men are more likely to delay seeking treatment. [225] Additionally, more females were found to have asthma in the cohort than males, with a higher proportion of females with asthma at the higher treatment steps in the study data, where patients are at higher risk of asthma exacerbations (Table 8-12).

Table 8-12. The proportion of males and females at each treatment step

	Step 2	Step 3	Step 4	Step 5
Male	44.53	42.43	41.75	36.40
Female	55.47	57.57	58.25	63.60

8.5.2.2 Prescription exemption

The results from Chapter 6, where exemption from payment was associated with higher adherence is not consistent with the results from this Chapter based on the intercept from the model, where adherence was observed to be lower for exempt patients. This intercept represents the effect of exemption on adherence without the effect of the patient variables that wereincluded in the model. However, many of the patient variables have a negative effect on adherence in the non-exempt patient group, which would reverse this observation for most patients. These include patients prescribed fluticasone and ciclesonide, patients treated at step 5 when compared with step 2, patients with poor control and those who had their treatment step increased. The reverse was observed for some variables where the adherence was lower in the exempt patients, these include patients prescribed budesonide, smokers, and patients who experienced a primary care exacerbation in the previous year, however, the effects of these variables are smaller than those lowering adherence for the non-exempt patients.

8.5.2.1 Socioeconomic status

The literature shows evidence of higher deprivation being associated with low adherence [63], however, the opposite association was found in Chapter 6 and in the modelling in this modelling chapter.

Patients who were recorded as living in an area that was classified as the most deprived were found to have the highest mean adherence. This was observed in the intercept calculated for each socioeconomic status in the modelling, however, many of the other variables included in the model have a reducing effect on PPR, especially in the most deprived patients when compared with the lowest, which could reverse this observed effect in many of the patient groups.

The patient variables, that were associated with lower adherence in the most deprived patients, consistently across the 2 models, were; treatment step 4, smoking and prescribed budesonide and fluticasone and poor control. Adherence was only lowered for patients in the least deprived group who were prescribed ciclesonide, which was a small number of patients compared with the other ICS's prescribed, and when patients had spent more years in the study.

The most deprived patients and patients with some specific comorbidities will have qualified to receive prescription payment exemption. Literature suggests that deprived patients are also more likely to have comorbidities, especially when physical and mental health were also considered. [212] Therefore, exemption and comorbidities are both likely to be related to the effect of socioeconomic status on adherence. These three variables could not be considered in the same model since they are all time independent variables.

8.5.2.1 Comorbidities

In the modelling, patients with one or more comorbidity were found to have a higher adherence, than the group with no comorbidities (only asthma). This was consistent with the Chapter 6 results and the evidence presented in Chapter 1, where it was suggested that patients adherence could be affected by other medicines being prescribed, [80] which is increasingly likely with diagnosed comorbidities. This increased adherence could be partially due to the method of measuring adherence using prescriptions, where patients with comorbidities are likely to have more frequent visits to their GP, where all of their medicine may be prescribed at each or most visits causing a higher PPR to be calculated for their prescribed ICS.

Very few patients had the highest score of 15-18, but for these patients the adherence was found to be very high.

For the patients with no comorbidities, adherence was lower when patients had experienced a primary care exacerbation and who had a higher treatment step, especially step 5, when compared with step 2. In patients with more than 1 comorbidity, adherence was lower than the patients with no comorbidities in patients who were treated at steps 3 or 4, were prescribed budesonide or fluticasone, in patients who had poor control and with a decrease in treatment step.

8.5.3 Model comparison

The patient variables included in both models 1 and 2 generally had very similar estimates for their effects on annual PPR in terms of the direction and the size of

their individual effect on adherence. However, some differences were observed that could be used to understand the partial effect of the variables on others.

Therefore, the results of both models were included in the results, model 1 to provide some information about differences that were not observed in the more complex model, and model 2 to provide the additional information about the effect on PPR of the extra variables included.

By comparing the estimates from the two models some extra information could be interpreted by comparing the size of the effect once the extra variables had been added. This highlighted the variables in model 1 that were co-dependent with variables added into model 2. For example the effect of treatment step was reduced, once the drug substances variables were included. This is logical since severity of asthma is likely to influence the ICS drug prescribed, however the BTS/SIGN asthma guidelines [3] do not specify which ICS to prescribe to patients, and often this is only specified in local guidance. However, many of these local guidance documents list beclometasone at step 2, changing to fluticasone at step 4, with ciclesonide or mometasone prescribed if the other ICS are unsuccessful or unsuitable. [226 227] The additional variables in the second model should make the estimation of adherence more accurate since unobserved heterogeneity was reduced.

In addition, when the models were sub grouped by gender or socioeconomic status, both the direction of the effect (lowering or increasing adherence) and the subgroup found to have the greatest effect caused by poor control was not consistent between the models. This suggests that the variable for poor control was

confounded by many other variables, some of which were captured in the more complex model.

An exacerbation recorded in the primary care data in the previous year increased adherence to ICS in patients with no comorbidities in the simple model. In the more complex model, the estimate for patients with 1 or more comorbidities was not significant, so could not be compared.

8.5.4 Strengths and limitations of the modelling methodology and estimation

This modelling and estimation method using the GMM estimator implemented using Roodman's xtabond2 algorithm [217] was able to estimate the effect of each individual time dependent variable on adherence including the feedback effect of adherence and clinical outcome from the previous years.

The large size of the cohort means that even small effects in adherence observed in the variables are likely to be significant, despite the specification test for the model being unsuitable.

The effect of the time variable (years in study) on adherence is estimated as a single number. This suggests that with every increasing year of the study, the effect of this increasing year is the same, i.e. the size of the effect of patient year number on adherence in consistent over time .i.e. assumes that the effect of time on PPR in linear. In Chapter 6 (Figure 6-2) an approximately linear relationship was observed in adherence over time, but this modelling does not provide information about how adherence changes differently between subgroups of these variables over the whole study duration.

The model used in this chapter is a simplified model of adherence, in reality, many other factors may affect adherence, and more complex relationships between the variables exist. For example, an increase in treatment step could affect the patient's adherence but conversely, a change in treatment step could be caused by a patient having poor control of their symptoms, caused by poor adherence. Another example is for smoking, where smoking was found to increase adherence, but would be expected to also affect clinical outcome.

Another limitation of the model is that the effect of time independent variables on adherence cannot be estimated within the model. To consider the effect of these variables, the patients were sub grouped by each variable group prior to running the model to observe any differences. Ideally all of the variables would have been included as independent variables and the individual effect on adherence of all variables would be able to be estimated. I am unaware of any models that can include both time independent and dependent variables, and none have been previously used in this field.

8.6 Conclusions

A large effect on adherence was noted with many of the variables in the model estimates. One of the largest factors effecting adherence was the effect of the previous year's adherence and to a lesser extent the year before, where PPR was estimated to be 0.5% higher for every 1% increase in PPR measured over the year before. Patients found to have poor control were estimated to have a PPR of 5% higher than patients with good control. Being treated with ciclesonide had a large

positive effect on adherence, with those patient prescribed budesonide also seeing a positive effect.

However those patients who were prescribed fluticasone had a lower estimated adherence. Being treated at a higher treatment step had a reasonably large negative effect on adherence, but an increase in step from the previous year had a similar size of positive effect on adherence. Older patients, those who were followed in the study for longer and smokers also had a higher estimate for adherence, as were patients who experienced an exacerbation during the previous year and patients who smoked.

The individual effect of being male rather than female, not being exempt from prescription payment and having a high socioeconomic status, also were associated with higher adherence, but these characteristics are often associated with other characteristics that were found to have a significant lowering effect on adherence.

An asthma exacerbation had an increased effect on adherence in the year following an exacerbation of asthma (of any severity).

Unexpectedly, but consistent with Chapter 6, it was noted that many of the variables that were found to be associated with lower adherence, were the patient variables associated with better health, or experienced no exacerbations of asthma (Table 8-13) with the exception of being treated at a higher treatment step, previous poor adherence and a primary care exacerbation occurring in the same year.

These results highlight the complex relationship between adherence and clinical outcome.

Table 8-13. Patient variables found to be asociated with low adherence to ICS in the dynamic panel model

General health	Asthma outcome	Other
Younger age	No exacerbation recorded in the previous year	Exempt from prescription payment
Fewer years in study	Higher treatment step	Female
Fewer comorbidities	Decrease in treatment step	Low deprivation
Non smoker	Good control	Prescribed fluticasone, not ciclesonide or budesonide or beclomethasone
	Lower previous adherence	

The dynamic panel model was a useful methodology to use to determine the effects of the time dependent variables on adherence. Its use could be extended to further studies in the field especially to study adherence. It is especially useful in studies where past values of the dependent and independent variables could affect future values, which need to be considered when estimating the model.

Chapter 9 Final discussion and conclusions

The aim of the study was to investigate what patient variables are associated with an asthma patient's adherence to ICS, and how these relationships change over treatment time. This was conducted using a large primary care dataset.

9.1 Main findings

Adherence for a patient was found to be dependent on its previous values and varied between patients with different characteristics and also influences patient outcome. The results are summarised in Appendix 22.

9.1.1 Characteristics of the cohort, adherence and clinical outcome

The study cohort (n=292738) included all asthma patients from in the CPRD between 1997 and 2010 who were aged 12 to 65 years, with no COPD records, at least one ICS prescribed per year, and who had records linked to HES secondary care data.

Patient variables could be derived from the CPRD data for the cohort, and most were found to be reasonably complete for patients including gender, region, and socioeconomic status, comorbidities, pregnancy, adverse effects of ICS, the prescribed ICS. Marital status and patient BMI were less well recorded.

The prevalence in the study cohort (5.4% of the estimated eligible CPRD population in 2010) and patient characteristics were found to be comparable to those that would be expected to be observed in the general population. Three or more years of data were available for 55% of the study cohort.

Following a number of data management steps, different methods to calculate PPR were compared and the method selected included overlapping days between prescriptions, passed excess days to the next interval (at the year-end), and gaps in the number of days prescribed in the denominator were considered. Once the PPR was calculated, it was censored at 100%. Adherence was able to be calculated for 99.7% of the patient years included in the study with a mean of 67.6%.

Patients experienced an exacerbation in 18% (212301 patients) of the patient years in the study. An exacerbation was classified at two severity levels; most exacerbations were only treated within primary care (96.5%) but some required secondary care treatment (3.5%). The proportion of the patients who had a recorded secondary care exacerbation generally decreased over time, especially between 1997 and 2002. However the proportion of patients who had a recorded primary care exacerbation stayed relatively constant until 2006, where the proportion increased. However, by time spent in the study cohort, the proportion of patients who experienced a secondary care exacerbation generally decreased over time (from approximately 0.8% at 1 year to 0.5% at 14 years) accompanied by an increase in the proportion of patients who experienced a primary care exacerbation (after an initial fall) from approximately 16% at 2 years to 21% at 13 years.

Patient asthma severity was measured by treatment step, based on the British asthma guidelines. [3] Most of the patients years included in the cohort were recorded as being treated within step 2 (55.38%), with very few patients recorded as being treated within step 5 (0.53%). From approximately 2001 the annual proportion of patients treated within step 2 and 4 decreased over calendar year.

The proportion of patients treated within step 3 increased over time Asthma severity increased throughout patients asthma treatment, shown by increase by study year observed in the proportion of patients treated at step 3, 4 and 5 and the and decrease in the proportion of patients treated at step 2.

Asthma control was measured by SABA use, where more than 10 doses of SABA prescribed per day indicated very poor asthma control. The proportion of patients with 'poor control' generally decreased by calendar year from 24% to 19% between 1997 and 2010. However by patient study year increased slightly up to year 14 of follow up (following a decreased in the first year).

The proportion of the study cohort who experienced an asthma exacerbation that was treated within primary or secondary increased with increasing treatment step, if their treatment step had been increased from the previous year and if they had been prescribed an average of over 10 doses of SABA prescribed per day. The proportion of patients with uncontrolled asthma was found to increase with increasing treatment step.

9.1.2 Factors influencing adherence

Mean PPR by calendar year was found to be relatively constant between 1997 and 2006, but increased until the end of the study in 2010. By patient year number an increase in mean PPR was observed throughout the study.

This finding that the longer patients were treated for asthma, the better they adhered to ICS is contrary to the limited previous research, which suggested that adherence often decreased with treatment time, [140 141] but the studies found were

much shorter over 12 and 24 months respectively. However, many of the relationships observed in this study can explain this trend of increasing PPR over time. The longer a patient was treated for their asthma, the more likely they were to be a patient who had a higher severity of asthma (as observed in the study data), and therefore they were more likely to also have experienced an exacerbation, in addition they will have been older in age as time progressed, a characteristic also associated with increased adherence.

When patients were sub grouped by their characteristics, lower mean adherence was often observed in patients with those characteristics that could be considered to be associated with better health, including; younger patients, non-smokers, patients with fewer comorbidities, patients with a BMI in the 'healthy' range, lower deprivation, patients who had experienced no exacerbation, good asthma control and lower asthma severity. Females, single patients and patients living in the East Midlands also had lower adherence.

Patient adherence generally increased over treatment time. Most of the characteristics studied were not found to affect this trend on adherence differently over time, with a few exceptions. The youngest patients, did not have the lowest adherence at the start of the study, but overall had the lowest mean adherence. Patients in the East Midlands started with the lowest adherence, but adherence increased at a faster rate than the other regions of England. Patients treated at step 2 started with the lowest adherence but increased at the fastest rate over time than the other severity groups. The proportion of patients who required primary care

treatment to treat an exacerbation increased over time and the proportion of patient requiring secondary care to treat their exacerbations decreased.

This increase in number of exacerbations treated within primary care was unexpected found alongside the observed increase in adherence over time. There are many possible reasons for this association. Patients who adhere to their prescribed ICS may be also more likely to access treatment within primary care to treat an exacerbation, thus preventing their need for secondary care treatment. This could also be due to the advances in treatments and treatment guidelines for asthma care within primary care or may be due to changes in the severity of asthma in the population over time.

Additionally, over time the severity of asthma in the cohort increased, which was also found to be associated with an increase in exacerbations. This may also make patients more likely to seek treatment earlier because they may learn to recognise early symptoms of an exacerbation or may be more aware of the importance of seeking early treatment.

9.1.3 Modelling adherence

Similar to the observations in chapter 6, many of the patient variables that were associated with a lower adherence to ICS were also the characteristics which could also be associated with better health, maybe because the patient did not believe that regular use of their medicines was necessary. [186] These included patients with a younger age (+0.11% per year) and fewer years in the study (+0.25% per year), non-smokers (-0.75%), who had a decrease in their asthma severity (-2.66%), who had good control of their asthma (low SABA use: -5.21%), who had experienced no

exacerbations in the previous year (primary care exacerbation: +0.87%, secondary care exacerbation: +1.45%), and those patients who had low deprivation (-3.1% for patients who were lease deprived compared with most deprived). Females were also associated with a lower adherence (-2.39% for females). A patient's future adherence was found to be influenced by previous adherence (0.50% in the previous year, and 0.10% for 2 years previous for every percentage increase in adherence).

However, in the modelling, some characteristics that could be associated with poorer general health were also found to be associated with lower adherence; exempt from prescription payment (-1.21%), and those who had more severe asthma (-3.32 for step 5, -0.64 for step 3). This was the opposite relationship was observed in Chapter 6.

Some of the effects of the patients' variables on PPR included in this analysis were consistent with previous evidence. These included age, prescription exemption, asthma severity, and a previous exacerbation treated within secondary care. For other patient's characteristics there is very little previous consistent evidence about the effect that we would expect to see on adherence to ICS. These included asthma control, the effect of a primary care, gender, smoking status, comorbidities, pregnancy, BMI, marital status, the region where the patient lives, adverse effects of ICS experienced and the drug substance prescribed.

9.1.4 Impact of adherence on the clinical outcome in asthma patients

Although many factors can affect patient outcome in asthma, adherence is one of the factors, alongside the healthcare system, that has the potential to be modified to try to improve patient outcome.

In this study, 32.5% of the patient years were found to have a PPR of 50% or less. A slightly higher proportion of these patients were found to have experienced an exacerbation if their PPR was below 50%, than those with above 50% PPR for patients treated within primary care (PPR and exacerbation was measured over the same year) and for secondary care.

However, this trend was not shown to be linear, where patients who had a PPR of 60% up to 100% had an increased risk of primary care exacerbation compared with patients who had a PPR below this level. Therefore, these patients still remained at a higher risk of experiencing an exacerbation despite high PPR. This may be partially due to the methods of measuring adherence (by PPR) and outcome, but it shows that what we believe to be 'good adherence' to ICS in asthma, i.e. a high PPR, does not always lead to a better patient outcome. This demonstrated that the prescribed treatments and regimens for asthma were not effective for all patients or that patient may be receiving their prescriptions, but not taking them. Outcomes in asthma are dependent on many factors as well as effective treatment and adherence to those treatments, some that were identified within this study such as asthma severity, and control.

A level of 50% PPR was used in this study as a cut off level for adherence, but this level can only be considered be a clinically relevant level of adherence for ICS for

this study, since there are many factors that would alter the relationship between the measured PPR and actual medicine taking. These include the data and methodology chosen for the study, but could also include changes in PPR or outcome caused by different patient variables. Some of these factors may be captured in the differences noted in adherence and outcome between other patient variables that were included in this study.

9.2 Review of the methodology used

Before the availability and use of large prescribing databases and the data linkage between primary and secondary care, adherence over time was difficult to study within the constraints of a RCT due to the potential for patients to modify their behaviour while being monitored, and the cost and practicality constraints of a large cohort, especially over a long period of time. Many studies have previously considered asthma or adherence, with or without changes over time, and sometimes included the variables that may affect adherence (Appendix 4). To my knowledge no studies have previously combined adherence to ICS in asthma patients and clinical outcome and the other patient variables over time in one study to enable us to understand, by modelling, the factors associated with changes adherence in asthma over time.

Because of the novel application of this data within this study, many different methods needed to be explored and tested to identify suitable measures for the variables, methods to use to visualise the effects of each variable on adherence, and to explore how these affected adherence over time.

9.3 The use of PPR to represent adherence

In order to study adherence using the CPRD data, first a method to define a suitable measure was required. The CPRD had not previously been used to define an adherence measure to ICS, and had not been used to define a repeated measure of adherence over time. Therefore, the options for defining adherence needed to be explored, and then alternative methods for deriving the selected measure needed to be tested to provide confidence in the suitability of the chosen method.

The PPR was selected to match the characteristics of asthma adherence and the data available for the study; medicines that were available to the patient (not treatment gaps), against a recorded prescribed daily dose, and using prescription records.

Repeated annual intervals to measure PPR were selected to be short enough to enable the investigation of changes in adherence over time, but to allow for seasonal changes within each year and to reduce the impact of any irregular prescribing of ICS, where patients may be prescribed several months of medicines at a time. Over the year, seasonal effects such as viruses, cold air, pollution or pollen could exacerbate patient's asthma symptoms which could make patients more likely to adhere to their controller medicines since they believe that their asthma is more severe and medicines are more necessary. [14]

Several different methods were compared to deal with missing data, overlapping doses, both between prescriptions and at the end of the years, and to allow for gaps in prescribing. However, at a cohort level, very little difference was found in the calculated adherence between the methods.

The development of this PPR measure using prescribing data to represent adherence to ICS in patients with asthma, enable rich data sources such as the CPRD and HES data to be used for this type of research, which has allowed long-term studies within routine clinical practice to provide insights into the actual use of these medicines in the UK population, which have not previously been possible. However there are some limitations of the methods, including most importantly that PPR does not measure the proportion of prescribed medicines actually taken by the patient, only the proportion of doses prescribed, which is expected to overestimate actual adherence. The PPR also relies on the assumption that a daily ICS was prescribed to the patient, in concordance with the BTS/ SIGN asthma guidelines as discussed previously. [3] Despite the limitations of these methods, and although not perfect, a PPR provides a suitable measure to represent adherence, especially useful to measure changes in adherence rather than absolute values.

9.4 Multiple approaches have demonstrated the complex relationships between the patient variables and adherence

Once the cohort and the variables were defined, the aim of the first method was to understand the difference in mean adherence between patients with different characteristics and how the mean adherence varied over time. Although simple, the bivariate analysis was able to show which patients, based on their characteristics, was more likely to have low adherence. This first method highlighted that patients with characteristics considered to be associated with better health were more likely to have lower adherence. This method, however, did not enable the effect of individual variables on adherence to be understood, since the effect of other patient variables may have contributed to the differences observed such as the

patient's asthma severity or outcome. Additionally, for time dependent variables such as exacerbation, it was impossible to establish whether any differences in adherence were caused by the exacerbation or were the cause of the exacerbation, when they were measured over the same time period. Therefore, it was important to investigate the effect of asthma outcome on adherence further.

To understand the relationship between adherence and exacerbation further, the first method in Chapter 7 looked at the effect of an asthma exacerbation on adherence, by comparing adherence in the year immediately prior to, and the year immediately following an exacerbation. A statistically significant increase in PPR was noted for both severities asthma exacerbation treatments within primary and secondary care. Using this method removed the uncertainty about when in the year that the exacerbation occurred, but it was still not possible to establish whether the patients increase in adherence was caused by the adherence being low before the exacerbation (causing the increased risk of exacerbation) or whether the exacerbation caused an increase in adherence.

The effect of adherence on clinical outcome investigated by graphically comparing the proportion of patients who had experienced an exacerbation with each level of adherence (rounded to the nearest percentage point) measured in the same and the previous year showed how a patient's likelihood of experiencing an exacerbation decreased with increasing PPR up to approximately 50% PPR (but the primary care exacerbation rate was higher again at higher PPR levels).

The next method using the relative risk of a patient experiencing an exacerbation with different levels of adherence (by PPR) provided results that were consistent

with the previous methods used where the relative risk of a patient experiencing an exacerbation was higher if they had a PPR of below the cut off level rather than above the cut off level, up to a cut off level of PPR of approximately 50%. This method was ideal for defining the cut off level for PPR, where PPR makes a clinically significant difference to a patient's risk of exacerbation.

The final method in Chapter 7 compared the PPR per patient year for patients who had and had not experienced an exacerbation and to compare the proportion of patients who experienced an exacerbation who had above and below the 50% PPR cut off level. This was the only method that allowed the effect of adherence clinical outcome and time to be plotted over time. A limitation of this method was having to use the PPR cut off level to be able to compare the 2 continuous variables, but the 50% cut of level was proven to be a significant level in the previous analysis.

In the preliminary investigations and the review of the literature, the relationship between the variables was found to be complex, where the effect of previous year's adherence, and previous outcome could affect adherence. All of the previous methodologies used in this study looked at the effect of PPR between patients with different characteristics, so the effects of each variable on adherence may have been biased by not controlling for other variables that may have affected this relationship.

To estimate the effect of the variables, including previous adherence and clinical outcome and up to 14 time points for a large number of patients, required a more complex method of regression than had previously been used within this field. This

led to the choice to trial the use of a panel regression model, estimated using the System generalised method of moments (system GMM).

This type of panel regression model allowed the effect of time dependent variables on adherence to be studied within one model, and provided estimates of the effect of these variables on adherence. The patients were not aggregated for the analysis, meaning that any differences in the effect on adherence between patients with different characteristics can be determined. [228] Previous values of the depend variable can also be used as regressors to try to remove the effects of unmeasured variables that change over time, and also provides an estimate of how time effects the dependent variable (adherence in this study).

Although the dynamic panel model has been used widely in the field of econometrics, [218] it has not been widely applied in health or epidemiology studies and I believe this is the first time that a has been used to model adherence in asthma.

The results from the analysis are at a population level, presented as the average difference that we would expect to see in adherence between patients with different characteristics. This is useful to provide information about what effects adherence at a macroeconomic level, which lends itself to informing policies or interventions rather than directing the individual treatment for patients, but it is maybe less appropriate to appropriately apply this average effect to individual patients.

The main advantage of the method GMM estimator to estimate the model is that it allowed past values of both the independent and dependent variables to be included in the model. However there are two main disadvantages of using the method, first time independent variables cannot be included in the model and the effect of time between years is defined as a single value, hence assumes that the effect of time in linear.

The modelling was able to provide the individual contribution that each variable made to a difference in adherence between patients, but was unable to show any differences in mean adherence between subgroups over time. Additionally before including the variables in the model, it was important to understand the variables and to understand how they should be included in the model, which also helps with the interpretation of the modelling results.

Interestingly, most of the conclusions about the effects of each patient characteristic on adherence were consistent between the methods used, with a few exceptions. This can increase our confidence in the results obtained.

The main value of using these methods together is that by combining them the full picture of the relationship between adherence and clinical outcome and how this relationship was affected by patient variables and time can begin to be understood. Although the data preparation for the analysis was lengthy, the same prepared variables could be used for all of the analysis methods.

9.5 Implications of this study

9.5.1 Implications of this study to clinical practice and policy

The influence that different patient variables have on mean PPR could be used to identify patient groups who are at risk of low adherence and could be used to develop guidelines for more efficient interventions to improve patient adherence to daily ICS, and consequently improve patient asthma control.

This study also reinforced the guideline recommendation that adherence should be reviewed before a patients treatment step is increased, [3] since it was found that patients treated at the higher treatment steps often had good control despite poor adherence, so could potentially have been treated with a lower dose of ICS if they did adhere. Patient inhaler technique and adherence to medicine should be regularly monitored within primary care, but should be checked before initiating a new drug therapy, [3] therefore adherence is most likely to be reviewed when a patients medicines are being reviewed, maybe following an exacerbation or has worsening of symptoms.

This study has shown that adherence increases in the year following an exacerbation, maybe due to this intervention. However, if instead the intervention preceded the exacerbation, the exacerbation may be able to be prevented. Therefore it would be useful to study the characteristics of patients who experienced an exacerbation. The could include adherence, but also characteristics such as poor control or severity.

From this study, it was clear that for most patients, increased adherence led to improved clinical outcome, where patients experienced fewer exacerbations.

However, some patients had good outcomes with poor adherence, questioning their need for the prescribed ICS. Other patients had poor outcome despite good adherence, which may question the efficacy of the prescribed treatment for the patients. This highlighted the importance for patients with either poor adherence or outcome, to have their treatment reviewed regularly to consider whether it is the most appropriate care for the patient.

The low levels of adherence identified in this study, make it clear that many patients and prescribers are not fully engaged with the guideline recommendations for daily ICS prescribing at the dose selected by the prescriber. This may be caused by the patient not requesting prescriptions, or by the prescriber not choosing to prescribe in line with the recorded daily dose.

There are many reasons for this. From the patient perspective, they may not feel that the medicine is necessary, they may forget to take their medicines, or they may have other barriers such as cost or access but these are likely to be associated the perception of the patient's condition. If the prescriber has chosen not to prescribe a daily dose to the patient, this may be appropriate to address the patient's individual needs, but this is not consistent with the treatment guideline recommendations. [3] This study has also shown that patients with better adherence experience fewer exacerbations.

An alternative cause of this low level of adherence may be that adherence was measured against a recorded daily dose requirement in the data, so therefore, if this record was inaccurate or a daily dose was not prescribed, the adherence estimate could be wrong. However, these data are from patient records, used to

record the patients treatment, so should be accurate to ensure safety for the patient.

In this study, patient adherence was found to be especially low at the beginning of treatment, but it was also found that patient's adherence was lowered when a change in treatment step was made (a decrease in treatment level). This has highlighted that patients may potentially need extra support during these changes to ensure that they adhere to their new treatment regime, not just at the beginning of treatment. In the UK, the new medicines service (NMS), introduced in October 2011, is available nationally within pharmacies for patients newly prescribed a medicine for a number of long-term conditions including asthma to help to improve adherence. [229] Medicine use reviews can also be offered to patients, however, the selection of patients for these reviews may not currently be targeted to the patients who and when would benefit most.

9.5.2 Implications of this study on future research

A large amount of overprescribing of ICS was observed in the study, where patients received over 365 days of medicine per year (seen for over 25% of the patients in the study). It would be useful to understand whether over prescribing benefits patients and is actually cost effective by comparing clinical outcome between patients that have 100% adherence and over 100% adherence. If no significant difference is observed, it can be assumed that patients do not actually take any more doses if they have over 100% of the days covered, and the over prescribing is an unnecessary cost.

However, if patients who have extra inhalers (over 100% annual adherence by PPR) have a decrease exacerbation rates, this could potentially represent a patient benefit and a cost saving to the NHS associated with this over prescribing, so may be appropriate. This may be because patients are more likely to have an inhaler available to be able to take their dose, or may be taking a dose exceeding the prescribed daily dose. If the latter is true, the increased dose would be improving clinical outcome, therefore the recorded prescribed daily dose may be lower than actually required to control the patient's asthma.

The analysis in this thesis was not able to assess the individual effect on PPR of variables on adherence over time when controlling for the effect of interactions between variables. Additionally, multiple time independent variables could not be considered in the same regression model. A model that could estimate the effects of each variable on adherence including both time and time independent variables together would be ideal, but may prove too complex to interpret.

In Chapter 6, adherence was measured in the year immediately before and after the occurrence of an asthma exacerbation. Adherence in the year after an exacerbation was found to be statistically higher than the year preceding the exacerbation. However, it would be interesting to investigate this further to understand how the adherence level compared in the 2 years before and after the exacerbation and maybe longer. This would enable the persistence of this increase after exacerbation to be understood and enable an understanding of whether adherence had dropped off stayed consistent before the occurrence of the exacerbation.

Finally, this study excluded elderly patients, this restriction was used to reduce the expected large variation expected to be seen between these patients and younger patients. However, elderly patients are prescribed approximately 50% of prescription medicines, but only represent 12-18% of the population. Therefore drug utilisation studies amongst this population are especially important.

The application of panel data modelling to pharmacoepidemiology studies is potentially a useful tool to utilise the data that is readily available in retrospective databases such as the CPRD which could be applied to adherence in many different conditions. There may be further models or methodologies that are used in different disciplines that could be applied to retrospective data from primary and secondary data to answer gaps in our current knowledge. This work would ideally be done collaboratively to ensure that the important research questions are being answered, and to provide appropriate data for the model to ensure that the methods of extraction and data management are clinically appropriate. Then the skills of a statistician or econometrician are important to select an appropriate method of estimation and together ensure that the results are interpreted appropriately.

9.6 Conclusion

This study has identified many patient treatment characteristics that are associated with different levels of adherence to ICS in asthma patients, and how this changes over a patient's treatment for asthma.

Many of the characteristics found to be associated with a lowering of adherence could also be associated with the patient's perception of their asthma, when they

may consider it to be less serious. These included; a decrease in step, no exacerbation, younger age, lower treatment step and earlier in the patients treatment. Therefore the findings of this study could also support the need for the development of interventions to help patients to understand their asthma, and what the consequences of non-adherence to ICS would be. It was also highlighted that patient adherence increased following an exacerbation, when patients may perceive their condition to be more serious.

These estimates could be used to identify the patient variables associated with low adherence to enable patient groups who are at higher risk of poor adherence and consequently those who were at higher risk of exacerbation to be identified. These patients could be targeted for interventions to try to help them to improve their adherence or to understand their adherence, hopefully before they experience an exacerbation.

This study was the first to use the CPRD data to define a suitable measure to represent adherence in asthma using a proxy for adherence, the prescription possession ratio (PPR). Although the PPR is not a perfect measure of adherence, it appears to represent changes in adherence well, when defined as the highest possible adherence level that the patient was exposed to. It measures how well patients follow the recommendations of the prescriber, and whether they request new prescriptions when necessary. However, this effect cannot be distinguished from a prescriber choosing not to prescribe a daily dose of ICS to the patient.

The use of a PPR allowed primary care databases, including prescribing data to be used. This allowed adherence to be studied in a UK clinical practice setting, over a

much longer timeframe that would be possible within a clinical trial. To use this data, methods needed to be adapted and developed to measure adherence and then to model the effect of the many available patient characteristic variables on adherence, including time, previous adherence and outcome. The panel model, estimated using a system generalised method of moments (system GMM) implemented using Roodman's xtabond2 algorithm, [217] was able to do estimate the effect of each variable on adherence, especially useful when considered at a population level.

Using a PPR measure using CPRD data opens up a new platform of data to use for adherence studies in asthma, which allowed us to study how multiple factors, measureable in the CPRD data affect this measure of adherence. Uniquely, by using the data available in the CPRD, the long-term effects of multiple variables on adherence can be measured in the UK using a large cohort from a routine clinical setting within primary and secondary care.

This study represents a good example of how the CPRD data can be used for this type of drug utilisation research, which could be adapted to be used across other conditions and to focus on more specific relationship between adherence and patient variables. Therefore, this study will hopefully further promote and support the validity use of primary care data to improve our understanding of the use and effectiveness of medicines in routine clinical practice, especially for long-term adherence studies where this information is not readily available from other sources.

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Appendices

Appendix. 1. Drug substances used in the treatment of chronic asthma from the Respiratory section of the BNF No. 62 (Sep 11)

	BNF chapter	Route	Drug Substance	ICS Dose equivalents
Short Acting Bronhodilators	Beta agonist-SABA (3.1.1.1 Selective beta2 agonists)	inhaled	Salbutamol	
		inhaled	terbutaline	
		inhaled	Fenoterol	
	Adrenoceptor agonists (3.1.1.2 Other adrenoceptor agonists)	inhaled	Ephedrine (should be avoided where possible as t is less selective)	
	Antimuscarinic bronchodilators (3.1.2 Antimuscarinic bronchodilators)	inhaled	ipratropium bromide	
	Xanthene derivitives (3.1.3 Theophylline)	tablets	theophylline	
			aminophylline	
Preventer Therapy	Steroids-ICS (3.2 Corticosteroids)	inhaled	Beclometasone (BDP)	400mcg (Qvar200-300mcg, Fostair-200mcg)
		inhaled	Budesonide	400mcg
		inhaled	Fluticasone	200mcg
		inhaled	Mometasone	200mcg
		inhaled	Ciclesonide	200-300mcg
	Beta agonist-LABA (3.1.1.1 Selective beta2 agonists)	inhaled	Formoterol	
		inhaled	Salmeterol	
		Inhaled/ tablet	Bambuterol	
	Mast cell stabilizers (3.3.1 Cromoglicate and related therapy)	inhaled	Sodium cromoglicate	
		inhaled	Nedocromil sodium	
	Leukotriene modifiers (3.3.2 Leukotriene receptor antagonists)	tablet	Montelukast	
		tablet	Zafirlukast	
	Xanthine derivitives (3.1.3 Theophylline)	tablet	MR Theophyllines	
	Anti IgE agents (Anti IgE monoclonal antibody) (3.4.2 Allergen immunotherapy)	injection	Omalizumab	
	Steroids- Oral steroids	tablet	Prednisolone	

Appendix 2. Summary of stepwise management of asthma

Step		Adult	Children aged 5-12 years	Children less than 5 years
1	**Mild intermittent asthma**	Inhaled short-acting β_2 agonist as required.	Inhaled short-acting β_2 agonist as required.	Inhaled short-acting β_2 agonist as required.
2	**Regular preventer therapy**	Add inhaled steroid 200-800 mcg/day.* 400 mcg is an appropriate starting dose for many patients. Start at dose of inhaled steroid appropriate to severity of disease.	Add inhaled steroid 200-400 mcg/ day.* 200 mcg is an appropriate starting dose for many patients. Start at dose of inhaled steroid appropriate to severity of disease.	Add inhaled steroid 200-400 mcg/day* or leukotriene receptor antagonist if inhaled steroid cannot be used. Start at dose of inhaled steroid appropriate to severity of disease.
3	**Initial add-on therapy**	1. Add LABA. 2. Assess control of asthma: - good response to LABA, continue LABA - benefit from LABA but control still inadequate- continue LABA and increase inhaled steroid dose to 800 mcg/day* (if not already on this dose) - no response to LABA, stop LABA and increase inhaled steroid to 800 mcg/ day.* If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or theophylline	1. Add inhaled LABA. 2. Assess control of asthma: -good response to LABA, continue LABA -Benefit from LABA but control still inadequate- continue LABA and increase inhaled steroid dose to 400 mcg/day* (if not already on this dose). - no response to LABA - stop LABA and increase inhaled steroid to 400 mcg/ day.* If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or theophylline	In those children taking inhaled steroid 200-400mcg/ day consider addition of leukotriene receptor antagonist. In those children taking leukotriene receptor antagonist alone reconsider addition of an inhaled steroid 200-400 mcg/day. In children under 2 years consider proceeding to step 4.
4	**Persistent poor control**	Consider trials of: - increasing inhaled steroid up to 2000 mcg/ day.* - Addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, β_2 agonist tablet.	Increase inhaled steroid up to 800 mcg/day.*	Refer to respiratory paediatrician.
5	**Continuous or frequent use of oral steroids**	Use daily steroid tablet in lowest dose providing adequate control. Maintain high dose inhaled steroid at 2000 mcg/ day.* Consider other treatments to minimise the use of steroid tablets Refer patient for specialist care	Use daily steroid tablet in lowest dose providing adequate control. Maintain high dose inhaled steroid at 800 mcg/ day.* Refer to respiratory paediatrician	* BDP or equivalent

Note: This table was adapted from The British Guideline on the Management of Asthma, 2014 [British Thoracic Society and Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma Oct 2014]

Appendix 3. Asthma severity classifications

Taken from the global initiative for asthma classifications [National Heart Lung and Blood Institute/ National Institutes of Health. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (NIH Publication No. 08-5846). . 2007]

Asthma classification	Symptoms/Day		Symptoms/Night	PEF or FEV1 PEF variability	BTS/ SIGN corresponding treatment step*
Intermittent	< 1 time a week	Asymptomatic and normal PEF between attacks	≤ 2 times a month	≥ 80% < 20%	1
Mild Persistent	> 1 time a week but < 1 time a day	Attacks may affect activity	> 2 times a month	≥ 80% 20-30%	2
Moderate Persistent	Daily	Attacks affect activity	> 1 time a week	60%-80% > 30%	3
Severe Persistent	Continuous	Limited physical activity	Frequent	≤ 60% > 30%	4 or 5

Uses National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, to

compare US treatment steps and prescribing guideline to the BTS/ SIGN treatment steps

Appendix 4. Studies using secondary data sets to calculate asthma adherence

yr	Authors	Coun-try	aim/ what measured	Data used	Study duration	Cohort size	Measure used	number of intervals	Result	Clinical outcome?	Other variables	cut off used?
2000	Kelloway *et al.* [108]	USA	Adherence before and after addition of salmeterol	prescribing and refill	8 months, (plus index period)	67	PPDC	2	49.7% before and 56.5% after	none	Salmeterol use, gender, age, dosing freq	no
2004	Stoloff *et al.[109]*	USA	Comparison of persistence to single and combined inhalers	refill	2 years (1 index year)	2511	MPR	2	combined 68.9.5, single 57.7%	none	not used with MPR Drug prescribed used Singe inhalers	no
2004	Williams L K, [76]	USA	To identify the proportion of poor outcome related to ICS non adherence.	refill	3 years (2 years and index year)	405 patients	MPR and CMG	1	CMA 50% CMG 54%	number or ED visits/ hospitilisations/oral steroid use	Number of LABA/ICS/SABA fills, sex, race, age, poor outcome	no
2005	Andersson K *et al.*, [119]	Swede n	Refill adherence using repeat prescriptions	refill	200 days (cross sectional)	47 prescrip-tions	MPR per prescriptio n	1	34%	none	yes, but reported for all conditions so not asthma specific, prescriber, age, gender, drug	<80%, >120%
2005	Stempel D A, [117]	USA	Comparison of adherence to fluticasone/ salmeterol combined and separate inhalers.	refill	2 years, (1 year as index period)	3503 subjects.	number of prescriptio ns in 30 days/ persistence (treatment days)	1	2.15-4.33 refills, 25.44-84.76 treatment days.	none	ICS/ SABA utilisation, age, gender, demographic, health plan, co morbidities, asthma hospitilisation, nebulizer use.	n/a
2006	Bender [110]	USA	Comparison of adherence to fluticasone/ salmeterol combined and separate inhalers	refill	12 months from first FSC prescriptio n	5504 patients	MPR	1	22%	none	Sex, age, co morbidities, copayment, previous LABA use, number of FCS, LABA use, co morbidities	n/a

yr	Authors	Coun-try	aim/ what measured	Data used	Study duration	Cohort size	Measure used	number of intervals	Result	Clinical outcome?	Other variables	cut off used?
2006	Marceau *et al.*, [103]	Canada	Comparison of adherence, persistence and effectiveness between groups taking combined and separate inhalers	refill	3 years Starting treatment, 2 years after ICS treatment (1999-2002)	5118 patients.	number of prescriptions/ persistence	1	5-10% were persistent after 1 year. Adherence-3.5 (combi) and 2.7(conc) prescriptions were filled	OCS prescription, hospitilisation, ED visit for asthma, (counted as 1 event if within 15 days)	Age, sex, social assistance, residency, ICS dose, prescriber specialty, severity measures I, SABA use/ week.	n/a
2006	Stern *et al*., [104]	USA	To investigate the association between adherence and exacerbation in asthma	Prescribing Managed care database	1 year after index date	97743	PDC (prescribing data?) Descrined as MPR Number of prescriptions	1	24%-for MPR 3.1 prescriptions	1 or more ED visits or hospitalisations within year	Sex, age at diagnosis/ 1st asthma prescription, region, payer type, product type, prescribers specialty, respiratory co morbidity, SABA use, OCS use	75%
2007	Williams *et al.* [113]	USA	To estimate rates of primary non adherence, adherence is measured for the year using the dispensing records.	refill data (but using information from prescribing)	at least 3 months	1064 patients	MPR (PPDC/ CMA)	1	46% 90% of prescriptions filled within 3 months	no	Age, sex, ethnicity, rescue medicine use,	grouped at 0%, , 1-80% and >80%
2007	Krigsman *et al.[114]*	Sweden	To measure refill adherence to ICS	refill	1994-2003	640 patients	MPR	1	59% of patients with undersupply and 12% with oversupply	no	age gender	80-120%
2008	Thier *et al.*[116]	USA	Determine the prevalence of patient adherence and provider adherence for chronic conditions	refill	180 days before and 90 days after index date	53470 adults, 8378 paeds	PDC (described as MPR)	1	paed-42% adults-37%	none	none	70%

yr	Authors	Coun-try	aim/ what measured	Data used	Study duration	Cohort size	Measure used	number of intervals	Result	Clinical outcome?	Other variables	cut off used?
2008	Menckeberg *et al [111]*	Nether lands	To investigate whether beliefs about ICS in questionnaires relate to adherence measured, also compares methods for measuring adherence	refill	1 year	238 patients returned questionnai re	MPR (described as CMA)	1	73.40%	none	Beliefs about medicines questionnaire (BMQ).	no
2009	Gamble *et al.* [105]	North ern Ireland	To investigate the prevalence of non adherence in difficult asthma and the effect on outcome	prescribing	6 months	182 patients	PPR- but not specified in text	1	35% of patients filled fewer than 50%, 21% filled greater than 100% of prescriptions	none	Hospital admissions, demographics, lung function, oral prednisolone use, QoL,	50%
2009	Haupt *et al.* [10]	Swede n	Adherence before and after initiation of a combination inhaler	refill	5 years (2000-2004)	815 patients	MPR	1	11-27% with satisfactory MPR. Higher in patients with combination products.	none	Age, sex, -prescribed ICS, LABA or a combination inhaler	80%
2010	Pando *et al.* [12]	Canad a	The effect of adherence/ use/ prescribing patterns of ICS	prescribing and refill	12 month index period and 12 month follow up.	2355	PPDC	1	152/365 days prescribed, PPDC 62.4%, PDC (based on dispensed data) 18.5%, 47.6% had no refill after their first ICS prescription.	OCS prescription (<=14 days), hospitalisation or ED visit for asthma, (counted as 1 event if within 15 days).	SABA use/ week, prescribing patterns, use of health care services, adherence, average daily dose of ICS	no
2010	Wilson *et al.* [112]	USA	Patients with poorly controlled asthma (US). Investigates the effect of shared and clinical decision making models on adherence	refill	2 years	612 patients	MPR	2	46% for CDM 67% for SDM	SABA use	Self reported asthma control, lung function,	no

yr	Authors	Coun-try	aim/ what measured	Data used	Study duration	Cohort size	Measure used	number of intervals	Result	Clinical outcome?	Other variables	cut off used?
2011	Blais, [91]	Canada	To develop the PPDC to understand the effect of suboptimal prescribing on the PDC measure.	prescribing and refill	2 years per patient	4190	PPDC	1	Mean PPDC was 52.6%, mean PDC was 19.1%. 41% of non-adherence could be attributed to non-prescribing of daily ICS,	OCS use, asthma ED visits, asthma hospitilisation, (if within 15 days counts as 1).	sex, area of residence, social assistance status, number of asthma outpatient visits, number of prescribers, Pulmonary function test, SABA use/ week	no
2011	Williams, LK *et al*., [106]	USA	To measure changes in adherence to ICS Over time and the effect on exacerbations	prescribing and refill	Average of 1.95 years, Moving 6 month period	298	PPDC	over time	26.30%. 24% of exacerbations attributed to non-adherence	Exacerbation, as a need for oral steroids, asthma related ED visit or hospitalisation	SABA use, gender, age, Asthma control at baseline FEV1, other asthma medicines prescribed	75%
2012	Elkout H *et al*. [107]	UK	To assess the association between asthma controller medication and asthma control	prescribing	between 1st and last prescriptio n	3172	PPR (described as MPR)	1	15-39% of patients had adequate adherence, under 80% in 51-69% of patients. Adherence not associated with less rescue medicine	>=1 OCS prescription, or >=6 SABA canisters pa	gender, SES,	80-120%
2012	Murphy AC *et al. [118]*	UK	Adherence compared with characteristics	prescribing	12 months before clinic appointme nt	161	PPDC	1	65.20%	hospitalisation, eosinophyl count/ ventilation	age, gender, race, smoking, dose prescribed	80%
2013	Rolnick *et al* [115]	USA	Assesses characteristics associated with adherence, 8 diseases	refill	1 year	15334, (2672 with asthma)	MPR	1	33% adherent (>080%)	none	age, gender, race, education, co morbidity	>=80%

Appendix 5. The CPRD files and data included in each

File name	Data included in file
Patient	Patient unique coded id (patid), gender, date of birth, marital status, family ID number, Child health surveillance number, prescription charge exemption, deprivation, date when patient first registered with the practice, transfer out dates and periods, death date and data acceptability indicator
Practice	Practice coded id, region, date of last collection for the practice and the date when the practice was considered to be u to research quality
Staff	Staff coded identification (staffid), gender and role
Consultation	Patid, event date (and the date it was added to the system), type of consultation, consultation identification number, staffid, duration of consultation
Clinical	Patid, event date (and the date it was added to the system), staff id, Consultation identification number, Medical code (Medcode#), free text, episode type and any additional information linked to this event
Referral	Patid, event date (and the date it was added to the system), staff id, Consultation identification number, medical code (Medcode*), free text, source of referral, referral specialty, referral type (in patient, day case etc.), description of type of event (first visit, follow up etc.), urgency
Test	Patid, event date (and the date it was added to the system), staff id, Consultation identification number, Medical code (Medcode#), free text, test results and unit of measure
Therapy	Patid, event date (and the date it was added to the system), staff id, Consultation identification number, Product code (Prodcode), free text, BNF code, quantity, numerical daily dose, number of days of treatment, number of packs, pack type, issue sequence of a repeat prescription

#The Medcode is a code used by the CPRD that can be linked to the medical Read code (via a CPRD look up file) to represent the medical term that was chosen by the GP to be recorded.
$ The Prodcode is a code used by the CPRD that can be linked to the Multilex product code (via a CPRD look up file) to represent the medicine/ product was chosen by the GP to be recorded.

Appendix 6. Read codes with the key word 'asthma'

Pegasus code	Read code	Description		Pegasus code	Read code	Description
5267	H331.00	Intrinsic asthma		8335	H33z111	Asthma attack NOS
7416	663N.00	Asthma disturbing sleep		11387	9OJ2.00	Refuses asthma monitoring
5798	H312000	Chronic asthmatic bronchitis		3458	663V000	Occasional asthma
31167	66YP.00	Asthma night-time symptoms		21232	H33zz12	Allergic asthma NEC
2290	H330.11	Allergic asthma		4606	H33zz11	Exercise induced asthma
1208	H330.12	Childhood asthma		38146	663N100	Asthma disturbs sleep weekly
15248	H330.13	Hay fever with asthma		26861	6.63E+02	Asthma sometimes restricts exercise
7731	H330.14	Pollen asthma		47993	66YZ.00	Does not have asthma management plan
93353	H35y600	Sequoiosis (red-cedar asthma)		58196	H331100	Intrinsic asthma with status asthmaticus
13173	663O.00	Asthma not disturbing sleep		73408	SLF7z00	Antiasthmatic poisoning NOS
92109	9NI8.00	Asthma outreach clinic		719	14B4.00	H/O: asthma
26506	6.63E+102	Asthma severely restricts exercise		98185	38DL.00	Asthma control test
29645	8793	Asthma control step 0		7191	663P.00	Asthma limiting activities
9663	66Y9.00	Step up change in asthma management plan		13064	663V.00	Asthma severity
5515	9N1d.00	Seen in asthma clinic		16667	8795	Asthma control step 2
10996	2126200	Asthma resolved		6707	H330111	Extrinsic asthma with asthma attack
5867	173A.00	Exercise induced asthma		47337	663m.00	Asthma accident and emergency attendance since last visit
31225	663t.00	Asthma causes daytime symptoms 1 to 2 times per month		9018	663y.00	Number of asthma exacerbations in past year
81	663..11	Asthma monitoring		19519	663p.00	Asthma treatment compliance unsatisfactory
26501	663s.00	Asthma never causes daytime symptoms		41017	1780	Aspirin induced asthma
42824	663q.00	Asthma daytime symptoms		30815	663N000	Asthma causing night waking
4892	H33z000	Status asthmaticus NOS		16070	H33zz00	Asthma NOS
20860	8798	Asthma control step 5		29325	H331000	Intrinsic asthma without status asthmaticus
13066	663h.00	Asthma - currently dormant		18141	66YE.00	Asthma monitoring due
19520	663n.00	Asthma treatment compliance satisfactory		23481	G581.11	Asthma - cardiac
8355	9OJA.11	Asthma monitored		25706	9OJ5.00	Asthma monitor 2nd letter
25181	663e.00	Asthma restricts exercise		54946	9OJ9.00	Asthma monitoring deleted
22752	173c.00	Occupational asthma		18224	8796	Asthma control step 3
13065	663V200	Moderate asthma		16785	8794	Asthma control step 1
1555	H33..11	Bronchial asthma		43770	13Y4.00	Asthma society member
93736	388t.00	Royal College of Physicians asthma assessment		10318	1J70.00	Suspected asthma
5609	68C3.00	Asthma screening		20422	9OJ..11	Asthma clinic administration
25705	9OJ6.00	Asthma monitor 3rd letter		3665	H331.11	Late onset asthma
6973	12D2.00	FH: Asthma		13176	66YK.00	Asthma follow-up
18763	8HTT.00	Referral to asthma clinic		11673	9hA1.00	Excepted from asthma quality indicators: Patient unsuitable
7146	H330.00	Extrinsic (atopic) asthma		63233	TJF7z00	Adverse reaction to antiasthmatic NOS
3366	663V300	Severe asthma		73522	173d.00	Work aggravated asthma

Pegasus code	Read code	Description		Pegasus code	Read code	Description
41554	9OJ3.00	Asthma monitor offer default		9552	66Y5.00	Change in asthma management plan
19167	66YQ.00	Asthma monitoring by nurse		55816	TJF7.00	Adverse reaction to antiasthmatics
51116	U60F600	[X]Antiasthmats cause adverse effects in therapeutic use, NEC		18176	ZV17500	[V]Family history of asthma
38144	663w.00	Asthma limits walking up hills or stairs		19539	9OJA.00	Asthma monitoring check done
24884	663u.00	Asthma causes daytime symptoms 1 to 2 times per week		45782	H330z00	Extrinsic asthma NOS
232	H33z100	Asthma attack		53812	ZVu6700	[X]Family history/asthma+other chronic lower resp diseases
38143	663O000	Asthma never disturbs sleep		30382	9OJZ.00	Asthma monitoring admin.NOS
14777	H330000	Extrinsic asthma without status asthmaticus		30308	9N4Q.00	DNA - Did not attend asthma clinic
5138	9Q21.00	Patient in asthma study		40864	U60F615	[X] Adverse reaction to theophylline - asthma
11370	1O2..00	Asthma confirmed		3018	663V100	Mild asthma
30458	66YR.00	Asthma monitoring by doctor		26503	663v.00	Asthma causes daytime symptoms most days
185	H333.00	Acute exacerbation of asthma		39478	H35y700	Wood asthma
11839	212G.00	Asthma resolved		13175	663N200	Asthma disturbs sleep frequently
47684	H47y000	Detergent asthma		10487	663j.00	Asthma - currently active
35927	8CE2.00	Asthma leaflet given		26504	663f.00	Asthma never restricts exercise
18323	H331111	Intrinsic asthma with asthma attack		45073	H331z00	Intrinsic asthma NOS
18692	9hA..00	Exception reporting: asthma quality indicators		233	H33z011	Severe asthma attack
78	H33..00	Asthma		11695	9hA2.00	Excepted from asthma quality indicators: Informed dissent
12987	H33z200	Late-onset asthma		13174	663Q.00	Asthma not limiting activities
25791	8CR0.00	Asthma clinical management plan		16655	9OJ..00	Asthma monitoring admin.
24506	8791	Further asthma - drug prevent.		5627	H330011	Hay fever with asthma
20886	8797	Asthma control step 4		37943	9OJ7.00	Asthma monitor verbal invite
10274	8B3j.00	Asthma medication review		46529	9OJ1.00	Attends asthma monitoring
39570	663r.00	Asthma causes night symptoms 1 to 2 times per month		7229	663W.00	Asthma prophylactic medication used
48591	TJF7300	Adverse reaction to theophylline (asthma)		7378	663U.00	Asthma management plan given
38145	663x.00	Asthma limits walking on the flat		31135	9OJ8.00	Asthma monitor phone invite
26496	679J.00	Health education - asthma		25707	9OJ4.00	Asthma monitor 1st letter
4442	H33z.00	Asthma unspecified		18223	66YA.00	Step down change in asthma management plan
25796	H332.00	Mixed asthma		41020	66YC.00	Absent from work or school due to asthma
40823	H334.00	Brittle asthma		7058	8H2P.00	Emergency admission, asthma
11022	178..00	Asthma trigger		10043	66YJ.00	Asthma annual review
27926	H330100	Extrinsic asthma with status asthmaticus		24479	663d.00	Emergency asthma admission since last appointment

Appendix 7. Asthma related product codes

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
8	salbutamol aerosol inhaler 100micrograms/inhalation	salbutamol sulphate	100micrograms /inhalation	aerosol inhaler	Inhalation	SABA
17	salbutamol cfc free inhaler 100micrograms/inhalation	salbutamol sulphate	100micrograms	cfc free inhaler	Inhalation	SABA
31	VENTOLIN aerosol inhaler 100micrograms/inhalation [GLAXO]	salbutamol sulphate	100micrograms	aerosol inhaler	Inhalation	SABA
38	beclometasone aerosol inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms	aerosol inhaler	Inhalation	Inhaled Corticosteroid
44	prednisolone enteric coated tablets 5mg	prednisolone	5mg	enteric coated tablets	Oral	Prednisolone
95	prednisolone tablets 5mg	prednisolone	5mg	tablets	Oral	Prednisolone
99	BECOTIDE 100 aerosol inhaler 100micrograms/actuation [A & H]	beclometasone dipropionate	100micrograms /	aerosol inhaler	Inhalation	Inhaled Corticosteroid
235	BRICANYL aerosol inhaler [ASTRAZENEC]	terbutaline sulphate		aerosol inhaler	Inhalation	SABA
282	salbutamol sugar free oral solution 2mg/5ml	salbutamol sulphate	2mg/5ml	sugar free oral solution	Oral	SABA
314	INTAL aerosol inhaler [AVENTIS]	sodium cromoglicate		aerosol inhaler	Inhalation	Chromones
326	DAVENOL linctus [WYETH PHAR]	carbinoxamine maleate/ephedrine hydrochloride/pholcodine		linctus	Oral	Adrenreceptor Agonist
454	PULMICORT aerosol inhaler 200micrograms [ASTRAZENEC]	budesonide	200micrograms	aerosol inhaler	Inhalation	Inhaled Corticosteroid
465	salmeterol aerosol inhaler 25micrograms/actuation	salmeterol xinafoate	25micrograms/	aerosol inhaler	Inhalation	Long acting beata agonist
510	VENTOLIN respirator solution 5mg/ml [A & H]	salbutamol sulphate	5mg/ml	respirator solution	Nebulised	SABA
534	ATROVENT aerosol inhaler 20micrograms/actuation [BOEH INGL]	ipratropium bromide	20micrograms/	aerosol inhaler	Inhalation	Antimuscarinic bronchodilator
549	SEREVENT aerosol inhaler 25micrograms/actuation [GLAXO]	salmeterol xinafoate	25micrograms/	aerosol inhaler	Inhalation	Long acting beata agonist
555	aminophylline modified release tablet 225mg	aminophylline hydrate	225mg	modified release tablet	Oral	Xanthines
556	COMBIVENT aerosol inhaler 20mcg + 100mcg [BOEH INGL]	ipratropium bromide/salbutamol sulphate	20mcg + 100mcg	aerosol inhaler	Inhalation	Antimuscarinic bronchodilator
557	prednisolone enteric coated tablets 2.5mg	prednisolone	2.5mg	enteric coated	Oral	Prednisolone

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
				tablets		
558	DIMOTANE PLUS sugar free elixir [WYETH PHAR]	brompheniramine maleate/pseudoephedrine hydrochloride		sugar free elixir	Oral	Adrenreceptor Agonist
578	prednisolone tablets 1mg	prednisolone	1mg	tablets	Oral	Prednisolone
590	PHYLLOCONTIN CONTINUS tablets 225mg [NAPPPHARM]	aminophylline hydrate	225mg	tablets	Oral	Xanthines
622	montelukast (as sodium salt) chewable tablet 4mg	montelukast sodium	4mg	chewable tablet	Oral	Leukotrienes
638	SERETIDE 250 ACCUHALER dry powder inhaler [GLAXO]	salmeterol xinafoate/fluticasone propionate		dry powder inhaler	Inhalation	Long acting beata agonist
665	SERETIDE 100 ACCUHALER dry powder inhaler [GLAXO]	salmeterol xinafoate/fluticasone propionate		dry powder inhaler	Inhalation	Long acting beata agonist
674	VENTOLIN NEBULES unit dose nebulising solution 2.5mg [A & H]	salbutamol sulphate	2.5mg	unit dose nebulising solution	Nebulised	SABA
695	SINGULAIR tablets 10mg [M S D]	montelukast sodium	10mg	tablets	Oral	Leukotrienes
696	salbutamol modified release capsules 8mg	salbutamol sulphate	8mg	modified release capsules	Oral	SABA
719	salmeterol dry powder inhaler 50micrograms/actuation	salmeterol xinafoate	50micrograms /actuation	dry powder inhaler	Inhalation	Long acting beata agonist
746	tiotropium capsules (for inhalation) 18 micrograms	tiotropium bromide monohydrate	18 micrograms	capsules (for inhalation)	Inhalation	Antimuscarinic bronchodilator
808	montelukast (as sodium salt) tablets 10mg	montelukast sodium	10mg	tablets	Oral	Leukotrienes
856	VENTOLIN syrup 2mg/5ml [A & H]	salbutamol sulphate	2mg/5ml	syrup	Oral	SABA
860	salbutamol tablets 4mg	salbutamol sulphate	4mg	tablets	Oral	SABA
862	SALBULIN aerosol inhaler [3M]	salbutamol sulphate		aerosol inhaler	Inhalation	SABA
863	SLO-PHYLLIN capsules 125mg [LIPHA]	theophylline	125mg	capsules	Oral	Xanthines
879	theophylline modified release capsules 125mg	theophylline	125mg	modified release capsules	Oral	Xanthines
880	theophylline modified release capsules 60mg	theophylline	60mg	modified release capsules	Oral	Xanthines
881	salbutamol tablets 2mg	salbutamol sulphate	2mg	tablets	Oral	SABA
882	salbutamol capsules (for inhalation) 200micrograms	salbutamol sulphate	200micrograms	capsules (for inhalation)	Inhalation	SABA
883	BECODISKS disc 200micrograms [A & H]	beclometasone dipropionate	200micrograms	disc	Inhalation	Inhaled Corticosteroid

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
895	BECLAZONE EASI-BREATHE breath actuated inhaler 100micrograms/actuation [IVAX]	beclometasone dipropionate	100micrograms / actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
896	BECOTIDE EASI-BREATHE breath actuated inhaler 100micrograms/actuation [A & H]	beclometasone dipropionate	100micrograms / actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
898	VENTOLIN EVOHALER 100micrograms/inhalation [GLAXO]	salbutamol sulphate	100micrograms / inhalation	EVOHALER	Inhalation	SABA
907	BRICANYL TURBOHALER 500micrograms [ASTRAZENEC]	terbutaline sulphate	500micrograms	TURBOHALER	Inhalation	SABA
908	PULMICORT TURBOHALER dry powder inhaler 400micrograms/actuation [ASTRAZENEC]	budesonide	400micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
909	budesonide aerosol inhaler 200micrograms/actuation	budesonide	200micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
910	SEREVENT DISKHALER 50micrograms [GLAXO]	salmeterol xinafoate	50micrograms	DISKHALER	Inhalation	Long acting beata agonist
911	FLIXOTIDE ACCUHALER 250micrograms/inhalation [A & H]	fluticasone propionate	250micrograms / inhalation	ACCUHALER	Inhalation	Inhaled Corticosteroid
925	DEPO-MEDRONE WITH LIDOCAINE injection 40mg/ml + 10mg/ml [PHARMACIA]	lidocaine hydrochloride/ methylprednisolone acetate	40mg/ml + 10mg/ml	injection	Periarticular Injection	n/a
942	AEROLIN AUTOHALER breath actuated inhaler 100micrograms/actuation [3M]	salbutamol sulphate	100micrograms / actuation	breath actuated inhaler	Inhalation	SABA
947	budesonide refill canister 50micrograms/actuation	budesonide	50micrograms/ actuation	refill canister	Inhalation	Inhaled Corticosteroid
955	prednisolone sodium phosphate soluble tablet 5mg	prednisolone sodium phosphate	5mg	soluble tablet	Oral	Prednisolone
956	PULMICORT TURBOHALER dry powder inhaler 200micrograms/actuation [ASTRAZENEC]	budesonide	200micrograms / actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
957	SALAMOL EASI-BREATHE breath actuated inhaler 100micrograms/actuation [IVAX]	salbutamol sulphate	100micrograms / actuation	breath actuated inhaler	Inhalation	SABA
958	VENTOLIN EASI-BREATHE breath actuated inhaler 100micrograms/actuation [A & H]	salbutamol sulphate	100micrograms / actuation	breath actuated inhaler	Inhalation	SABA
959	budesonide aerosol inhaler 50micrograms/actuation	budesonide	50micrograms/ actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
960	PULMICORT TURBOHALER dry powder inhaler 100micrograms/actuation [ASTRAZENEC]	budesonide	100micrograms / actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
964	sodium cromoglicate aerosol inhaler 5mg/inhalation	sodium cromoglicate	5mg/inhalation	aerosol inhaler	Inhalation	Chromones
987	VENTOLIN tablets 4mg [A & H]	salbutamol sulphate	4mg	tablets	Oral	SABA
1063	PREDNESOL tablets 5mg [SOVEREIGN]	prednisolone sodium	5mg	tablets	Oral	Prednisolone

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
		phosphate				
1087	ASMASAL CLICKHALER dry powder inhaler 95micrograms [UCB]	salbutamol sulphate	95micrograms	dry powder inhaler	Inhalation	SABA
1093	SALAMOL aerosol inhaler 100micrograms/actuation [IVAX]	salbutamol sulphate	100micrograms /actuation	aerosol inhaler	Inhalation	SABA
1097	SLO-PHYLLIN capsules 60mg [LIPHA]	theophylline	60mg	capsules	Oral	Xanthines
1100	BECLAZONE aerosol inhaler 100micrograms/actuation [IVAX]	beclometasone dipropionate	100micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1133	DEPO-MEDRONE injection 40mg/ml [PHARMACIA]	methylprednisolone acetate	40mg/ml	injection	Periarticular Injection	n/a
1236	BECLOFORTE aerosol inhaler 250micrograms/actuation [A & H]	beclometasone dipropionate	250micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1242	beclometasone aerosol inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1243	BECLAZONE EASI-BREATHE breath actuated inhaler 250micrograms/actuation [IVAX]	beclometasone dipropionate	250micrograms / actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
1258	BECOTIDE 200 aerosol inhaler 200micrograms/actuation [A & H]	beclometasone dipropionate	200micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1259	beclometasone aerosol inhaler 200micrograms/actuation	beclometasone dipropionate	200micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1269	BECOTIDE nebuliser suspension 50micrograms/ml [A & H]	beclometasone dipropionate	50micrograms/ ml	nebuliser suspension	Nebulised	Inhaled Corticosteroid
1346	salbutamol injection 0.05mg/ml	salbutamol sulphate	0.05mg/ml	injection	Unknown	SABA
1406	BECOTIDE 50 aerosol inhaler 50micrograms/actuation [A & H]	beclometasone dipropionate	50micrograms/ actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1409	ipratropium bromide aerosol inhaler 20micrograms/dose	ipratropium bromide	20micrograms/ dose	aerosol inhaler	Inhalation	Antimuscarinic bronchodilator
1410	ipratropium bromide nebuliser solution 0.25mg/ml	ipratropium bromide	0.25mg/ml	nebuliser solution	Nebulised	Antimuscarinic bronchodilator
1411	ipratropium bromide unit dose nebulising solution 250micrograms/ml	ipratropium bromide	250micrograms / ml	unit dose nebulising solution	Nebulised	Antimuscarinic bronchodilator
1412	FLIXOTIDE aerosol inhaler 250micrograms/actuation [A & H]	fluticasone propionate	250micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1414	STERI-NEB SALAMOL unit dose nebulising solution 5mg/2.5ml [IVAX]	salbutamol sulphate	5mg/2.5ml	unit dose nebulising	Nebulised	SABA

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
				solution		
1415	STERI-NEB IPRATROPIUM unit dose nebulising solution 250micrograms/ml [IVAX]	ipratropium bromide	250micrograms /ml	unit dose nebulising solution	Nebulised	Antimuscarinic bronchodilator
1422	CROMOGEN aerosol inhaler 5mg/inhalation [IVAX]	sodium cromoglicate	5mg/inhalation	aerosol inhaler	Inhalation	Chromones
1423	UNIPHYLLIN CONTINUS prolonged release tablet 200mg [NAPPPHARM]	theophylline	200mg	prolonged release tablet	Oral	Xanthines
1424	FLIXOTIDE disc 250micrograms [A & H]	fluticasone propionate	250micrograms	disc	Inhalation	Inhaled Corticosteroid
1426	FLIXOTIDE disc 500micrograms [A & H]	fluticasone propionate	500micrograms	disc	Inhalation	Inhaled Corticosteroid
1518	FLIXOTIDE aerosol inhaler 50micrograms/actuation [A & H]	fluticasone propionate	50micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1537	BECOTIDE ROTACAPS 200micrograms [A & H]	beclometasone dipropionate	200micrograms	ROTACAPS	Inhalation	Inhaled Corticosteroid
1551	BECLAZONE aerosol inhaler 250micrograms/actuation [IVAX]	beclometasone dipropionate	250micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1552	BECLOFORTE EASI-BREATHE breath actuated inhaler 250micrograms/actuation [A & H]	beclometasone dipropionate	250micrograms / actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
1619	terbutaline dry powder inhaler 500micrograms	terbutaline sulphate	500micrograms	dry powder inhaler	Inhalation	SABA
1620	terbutaline aerosol inhaler 250micrograms/actuation	terbutaline sulphate	250micrograms / actuation	aerosol inhaler	Inhalation	SABA
1628	terbutaline refill canister 250micrograms/actuation	terbutaline sulphate	250micrograms / actuation	refill canister	Inhalation	SABA
1629	INTAL nebuliser solution 10mg/ml [AVENTIS]	sodium cromoglicate	10mg/ml	nebuliser solution	Nebulised	Chromones
1630	salbutamol unit dose nebulising solution 2.5mg/2.5ml	salbutamol sulphate	2.5mg/2.5ml	unit dose nebulising solution	Nebulised	SABA
1635	SALBUVENT syrup 2mg/5ml [PHARMACIA]	salbutamol sulphate	2mg/5ml	syrup	Oral	SABA
1642	budesonide dry powder inhaler 400micrograms/actuation	budesonide	400micrograms / actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
1676	FLIXOTIDE aerosol inhaler 125micrograms/actuation [A & H]	fluticasone propionate	125micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1680	PULMICORT LS aerosol inhaler 50micrograms [ASTRAZENEC]	budesonide	50micrograms	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1683	INTAL SPINCAPS inhalation powder capsules [AVENTIS]	sodium cromoglicate		inhalation powder capsules	Inhalation	Chromones
1697	ATROVENT AUTOHALER breath actuated inhaler 20micrograms/actuation [BOEH INGL]	ipratropium bromide	20micrograms/ actuation	breath actuated inhaler	Inhalation	Antimuscarinic bronchodilator

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
1698	salbutamol breath actuated inhaler 100micrograms/actuation	salbutamol sulphate	100micrograms /actuation	breath actuated inhaler	Inhalation	SABA
1711	salbutamol unit dose nebulising solution 5mg/2.5ml	salbutamol sulphate	5mg/2.5ml	unit dose nebulising solution	Nebulised	SABA
1725	BECLAZONE EASI-BREATHE breath actuated inhaler 50micrograms/actuation [IVAX]	beclometasone dipropionate	50micrograms/ actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
1727	BECOTIDE EASI-BREATHE breath actuated inhaler 50micrograms/actuation [A & H]	beclometasone dipropionate	50micrograms/ actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
1728	CROMOGEN EASI-BREATHE breath actuated inhaler 5mg/inhalation [IVAX]	sodium cromoglicate	5mg/inhalation	breath actuated inhaler	Inhalation	Chromones
1734	beclometasone breath actuated inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms /actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
1741	salbutamol cfc free breath actuated inhaler 100micrograms/actuation	salbutamol sulphate	100micrograms /actuation	cfc free breath actuated inhaler	Inhalation	SABA
1794	BEROTEC aerosol inhaler 100micrograms/actuation [BOEH INGL]	fenoterol hydrobromide	100micrograms / actuation	aerosol inhaler	Inhalation	SABA
1801	VENTIDE aerosol inhaler [A & H]	beclometasone dipropionate/salbutamol		aerosol inhaler	Inhalation	Inhaled Corticosteroid
1832	THEOGRAD tablets 350mg [ABBOTT]	theophylline	350mg	tablets	Oral	Xanthines
1833	theophylline modified release tablet 200mg	theophylline	200mg	modified release tablet	Oral	Xanthines
1834	theophylline modified release tablet 400mg	theophylline	400mg	modified release tablet	Oral	Xanthines
1861	AEROBEC AUTOHALER 100micrograms/actuation [MEDA]	beclometasone dipropionate	100micrograms / actuation	AUTOHALER	Inhalation	Inhaled Corticosteroid
1882	VENTODISKS disc 200micrograms/blister [A & H]	salbutamol sulphate	200micrograms / blister	disc	Inhalation	SABA
1885	BECLAZONE aerosol inhaler 200micrograms/actuation [IVAX]	beclometasone dipropionate	200micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
1950	VENTODISKS disc 400micrograms/blister [A & H]	salbutamol sulphate	400micrograms / blister	disc	Inhalation	SABA
1951	BECODISKS disc 400micrograms [A & H]	beclometasone dipropionate	400micrograms	disc	Inhalation	Inhaled Corticosteroid
1952	VENTOLIN ROTACAPS 400micrograms [A & H]	salbutamol sulphate	400micrograms	ROTACAPS	Inhalation	SABA
1956	PULMICORT RESPULES nebuliser suspension 1mg/2ml [ASTRAZENEC]	budesonide	1mg/2ml	nebuliser suspension	Nebulised	Inhaled Corticosteroid

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
1957	VENTOLIN NEBULES unit dose nebulising solution 5mg [A & H]	salbutamol sulphate	5mg	unit dose nebulising solution	Nebulised	SABA
1959	PULMICORT RESPULES nebuliser suspension 0.5mg/2ml [ASTRAZENEC]	budesonide	0.5mg/2ml	nebuliser suspension	Nebulised	Inhaled Corticosteroid
1960	VOLMAX tablets 8mg [A & H]	salbutamol sulphate	8mg	tablets	Oral	SABA
1961	VOLMAX tablets 4mg [A & H]	salbutamol sulphate	4mg	tablets	Oral	SABA
1962	ATROVENT UDVs nebuliser solution 0.25mg/ml [BOEH INGL]	ipratropium bromide	0.25mg/ml	nebuliser solution	Nebulised	Antimuscarinic bronchodilator
1973	ACCOLATE tablets 20mg [ASTRAZENEC]	zafirlukast	20mg	tablets	Oral	Leukotrienes
1974	OXIS 12 TURBOHALER dry powder inhaler 12micrograms/actuation [ASTRAZENEC]	formoterol fumarate dihydrate	12micrograms /actuation	dry powder inhaler	Inhalation	Long acting beata agonist
1975	OXIS 6 TURBOHALER dry powder inhaler 6 micrograms/actuation [ASTRAZENEC]	formoterol fumarate dihydrate	6 micrograms/ actuation	dry powder inhaler	Inhalation	Long acting beata agonist
2020	BEROTEC aerosol inhaler 200micrograms/actuation [BOEH INGL]	fenoterol hydrobromide	200micrograms / actuation	aerosol inhaler	Inhalation	SABA
2090	DIMOTANE PLUS LA tablets [WYETH PHAR]	brompheniramine maleate/ pseudoephedrine hydrochloride		tablets	Oral	Adrenreceptor Agonist
2092	budesonide dry powder inhaler 200micrograms/actuation	budesonide	200micrograms / actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
2125	PULMICORT refill canister 200micrograms [ASTRAZENEC]	budesonide	200micrograms	refill canister	Inhalation	Inhaled Corticosteroid
2147	theophylline modified release capsules 250mg	theophylline	250mg	modified release capsules	Oral	Xanthines
2148	beclometasone disc 400micrograms	beclometasone dipropionate	400micrograms	disc	Inhalation	Inhaled Corticosteroid
2152	ipratropium bromide with salbutamol aerosol inhaler 20mcg + 100mcg	ipratropium bromide/salbutamol sulphate	20mcg + 100mcg	aerosol inhaler	Inhalation	Antimuscarinic bronchodilator
2158	sodium cromoglicate breath actuated inhaler 5mg/inhalation	sodium cromoglicate	5mg/inhalation	breath actuated inhaler	Inhalation	Chromones
2159	AEROBEC AUTOHALER 50micrograms/actuation [MEDA]	beclometasone dipropionate	50micrograms /actuation	AUTOHALER	Inhalation	Inhaled Corticosteroid
2160	beclometasone breath actuated inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/ actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
2224	SEREVENT ACCUHALER 50micrograms/actuation [GLAXO]	salmeterol xinafoate	50micrograms/ actuation	ACCUHALER	Inhalation	Long acting beata agonist
2229	BECODISKS disc 100micrograms [A & H]	beclometasone dipropionate	100micrograms	disc	Inhalation	Inhaled Corticosteroid

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
2282	fluticasone dry powder inhaler 500micrograms/inhalation	fluticasone propionate	500micrograms / inhalation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
2335	QVAR cfc free inhaler 100micrograms/actuation [IVAX]	beclometasone dipropionate	100micrograms /actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
2368	prednisolone tablets 2.5mg	prednisolone	2.5mg	tablets	Oral	Prednisolone
2440	FLIXOTIDE ACCUHALER 500micrograms/inhalation [A & H]	fluticasone propionate	500micrograms /inhalation	ACCUHALER	Inhalation	Inhaled Corticosteroid
2600	beclometasone breath actuated inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms /actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
2609	FRANOL tablets [SANOFI S]	ephedrine hydrochloride/theophylline		tablets	Oral	Adrenreceptor Agonist
2610	INTAL COMPOUND capsules (for inhalation) [RHONE]	isoprenaline sulphate/sodium cromoglicate		capsules (for inhalation)	Inhalation	Chromones
2655	AIROMIR cfc free inhaler 100micrograms/inhalation [TEVA]	salbutamol sulphate	100micrograms / inhalation	cfc free inhaler	Inhalation	SABA
2704	prednisolone tablets 25mg	prednisolone	25mg	tablets	Oral	Prednisolone
2722	DUOVENT aerosol inhaler 40micrograms + 100micrograms/actuation [BOEH INGL]	fenoterol hydrobromide/ipratropium bromide	40micrograms + 100micrograms /actuation	aerosol inhaler	Inhalation	SABA
2723	fluticasone aerosol inhaler 25micrograms/actuation	fluticasone propionate	25micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
2757	SLO-PHYLLIN capsules 250mg [LIPHA]	theophylline	250mg	capsules	Oral	Xanthines
2758	BRICANYL refill canister [ASTRAZENEC]	terbutaline sulphate		refill canister	Inhalation	SABA
2792	ketotifen sugar free elixir 1mg/5ml	ketotifen hydrogen fumarate	1mg/5ml	sugar free elixir	Oral	anti histamine
2850	salbutamol capsules (for inhalation) 400micrograms	salbutamol sulphate	400micrograms	capsules (for inhalation)	Inhalation	SABA
2851	VENTOLIN ROTACAPS 200micrograms [A & H]	salbutamol sulphate	200micrograms	ROTACAPS	Inhalation	SABA
2862	DUOVENT AUTOHALER breath actuated inhaler [BOEH INGL]	fenoterol hydrobromide/ ipratropium bromide		breath actuated inhaler	Inhalation	SABA
2869	salbutamol modified release tablet 8mg	salbutamol sulphate	8mg	modified release tablet	Oral	SABA
2892	BECLOFORTE disks (refill pack) 400micrograms/actuation [A & H]	beclometasone dipropionate	400micrograms / actuation	disks (refill pack)	Inhalation	Inhaled Corticosteroid
2893	beclometasone disc 200micrograms	beclometasone dipropionate	200micrograms	disc	Inhalation	Inhaled Corticosteroid
2911	sodium cromoglicate capsules (for inhalation) 20mg	sodium cromoglicate	20mg	capsules (for inhalation)	Inhalation	Chromones

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
2951	fluticasone aerosol inhaler 250micrograms/actuation	fluticasone propionate	250micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
2978	salbutamol dry powder inhaler 200micrograms/actuation	salbutamol sulphate	200micrograms / actuation	dry powder inhaler	Inhalation	SABA
2992	BECLAZONE aerosol inhaler 50micrograms/actuation [IVAX]	beclometasone dipropionate	50micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
2994	ATROVENT AEROCAPS 40mcg [BOEH INGL]	ipratropium bromide	40mcg	AEROCAPS	Inhalation	Antimuscarinic bronchodilator
2995	NUELIN SA tablets 175mg [MEDA]	theophylline	175mg	tablets	Oral	Xanthines
3018	beclometasone aerosol inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/ actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
3075	BECOTIDE ROTACAPS 400micrograms [A & H]	beclometasone dipropionate	400micrograms	ROTACAPS	Inhalation	Inhaled Corticosteroid
3119	BECLOFORTE INTEGRA inhaler with compact spacer 250micrograms/actuation [GLAXO]	beclometasone dipropionate	250micrograms / actuation	inhaler with compact spacer	Inhalation	Inhaled Corticosteroid
3150	beclometasone extra fine particle cfc free inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms / actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
3163	salbutamol disc 200micrograms	salbutamol sulphate	200micrograms	disc	Inhalation	SABA
3220	QVAR AUTOHALER cfc free breath actuated inhaler 50micrograms/actuation [IVAX]	beclometasone dipropionate	50micrograms/ actuation	cfc free breath actuated inhaler	Inhalation	Inhaled Corticosteroid
3254	SALBULIN tablets 4mg [3M]	salbutamol sulphate	4mg	tablets	Oral	SABA
3289	FLIXOTIDE aerosol inhaler 25micrograms/actuation [A & H]	fluticasone propionate	25micrograms/ actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
3297	salmeterol disc 50micrograms	salmeterol xinafoate	50micrograms	disc	Inhalation	Long acting beata agonist
3305	COMBIVENT UDVs nebuliser solution 2.5ml [BOEH INGL]	ipratropium bromide/salbutamol sulphate	2.5ml	nebuliser solution	Nebulised	Antimuscarinic bronchodilator
3306	ATROVENT FORTE aerosol inhaler 40micrograms/actuation [BOEH INGL]	ipratropium bromide	40micrograms/ actuation	aerosol inhaler	Inhalation	Antimuscarinic bronchodilator
3345	SINTISONE tablets [PHARMACIA]	prednisolone steaglate		tablets	Oral	Prednisolone
3363	BECLOFORTE DISKHALER 400micrograms/actuation [A & H]	beclometasone dipropionate	400micrograms / actuation	DISKHALER	Inhalation	Inhaled Corticosteroid
3374	ketotifen tablets 1mg	ketotifen hydrogen fumarate	1mg	tablets	Oral	anti histamine
3388	theophylline modified release tablet 175mg	theophylline	175mg	modified release tablet	Oral	Xanthines
3443	SALBUTAMOL SPACEHALER 100micrograms/inhalation [CELLTECH]	salbutamol	100micrograms / inhalation	SPACEHALER	Inhalation	SABA

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
3534	BRICANYL tablets 5mg [ASTRAZENEC]	terbutaline sulphate	5mg	tablets	Oral	SABA
3546	QVAR cfc free inhaler 50micrograms/actuation [IVAX]	beclometasone dipropionate	50micrograms/ actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
3556	beclometasone with salbutamol aerosol inhaler 50micrograms + 100micrograms/inhalation	beclometasone dipropionate/salbutamol	50micrograms + 100micrograms /inhalation	aerosol inhaler	Unknown	Inhaled Corticosteroid
3570	budesonide refill canister 200micrograms/actuation	budesonide	200micrograms / actuation	refill canister	Inhalation	Inhaled Corticosteroid
3584	BRICANYL sugar free oral solution 1.5mg/5ml [ASTRAZENEC]	terbutaline sulphate	1.5mg/5ml	sugar free oral solution	Oral	SABA
3585	STERI-NEB CROMOGEN nebuliser solution 10mg/ml [IVAX]	sodium cromoglicate	10mg/ml	nebuliser solution	Nebulised	Chromones
3666	SERETIDE 500 ACCUHALER dry powder inhaler [GLAXO]	salmeterol xinafoate/fluticasone propionate		dry powder inhaler	Inhalation	Long acting beata agonist
3688	TILADE mint inhaler 2mg/inhalation [SANOFI/AVE]	nedocromil sodium	2mg/inhalation	mint inhaler	Inhalation	Chromones
3743	FILAIR aerosol inhaler 50micrograms/actuation [MEDA]	beclometasone dipropionate	50micrograms/ actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
3786	fenoterol with ipratropium bromide aerosol inhaler 100micrograms + 40micrograms/actuation	fenoterol hydrobromide/ipratropium bromide	100micrograms + 40micrograms/ actuation	aerosol inhaler	Inhalation	SABA
3787	ZADITEN tablets 1mg [NOV/SANDOZ]	ketotifen hydrogen fumarate	1mg	tablets	Oral	anti histamine
3927	FILAIR aerosol inhaler 100micrograms/actuation [MEDA]	beclometasone dipropionate	100micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
3947	BECOTIDE ROTACAPS 100micrograms [A & H]	beclometasone dipropionate	100micrograms	ROTACAPS	Inhalation	Inhaled Corticosteroid
3989	FLIXOTIDE disc 100micrograms [A & H]	fluticasone propionate	100micrograms	disc	Inhalation	Inhaled Corticosteroid
3993	FILAIR FORTE aerosol inhaler 250micrograms/actuation [MEDA]	beclometasone dipropionate	250micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
3994	salbutamol modified release tablet 4mg	salbutamol sulphate	4mg	modified release tablet	Oral	SABA
4055	SALBULIN syrup 2mg/5ml [3M]	salbutamol sulphate	2mg/5ml	syrup	Oral	SABA
4100	INTAL AUTOHALER 5mg/inhalation [AVENTIS]	sodium cromoglicate	5mg/inhalation	AUTOHALER	Inhalation	Chromones
4131	fluticasone disc 100micrograms	fluticasone propionate	100micrograms	disc	Inhalation	Inhaled Corticosteroid
4132	fluticasone aerosol inhaler 125micrograms/actuation	fluticasone propionate	125micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
4171	VENTOLIN tablets 2mg [A & H]	salbutamol sulphate	2mg	tablets	Oral	SABA

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
4222	BRICANYL respirator solution 10mg/ml [ASTRAZENEC]	terbutaline sulphate	10mg/ml	respirator solution	Nebulised	SABA
4268	ipratropium bromide aerosol inhaler 40micrograms/metered inhalation	ipratropium bromide	40micrograms/ metered inhalation	aerosol inhaler	Inhalation	Antimuscarinic bronchodilator
4360	DIMOTANE PLUS PAEDIATRIC sugar free elixir [WYETH PHAR]	brompheniramine maleate/ pseudoephedrine hydrochloride		sugar free elixir	Oral	Adrenreceptor Agonist
4365	beclometasone disc 100micrograms	beclometasone dipropionate	100micrograms	disc	Inhalation	Inhaled Corticosteroid
4413	QVAR AUTOHALER cfc free breath actuated inhaler 100micrograms/actuation [IVAX]	beclometasone dipropionate	100micrograms /actuation	cfc free breath actuated inhaler	Inhalation	Inhaled Corticosteroid
4497	VENTOLIN ACCUHALER 200micrograms/actuation [GLAXO]	salbutamol sulphate	200micrograms / actuation	ACCUHALER	Inhalation	SABA
4499	AEROBEC forte AUTOHALER 250micrograms/actuation [MEDA]	beclometasone dipropionate	250micrograms / actuation	forte AUTOHALER	Inhalation	Inhaled Corticosteroid
4514	aminophylline modified release tablet 350mg	aminophylline hydrate	350mg	modified release tablet	Oral	Xanthines
4541	BRICANYL SA tablets 7.5mg [ASTRAZENEC]	terbutaline sulphate	7.5mg	tablets	Oral	SABA
4545	PULMICORT LS refill canister 50micrograms [ASTRAZENEC]	budesonide	50micrograms	refill canister	Inhalation	Inhaled Corticosteroid
4593	theophylline tablets 125mg	theophylline	125mg	tablets	Oral	Xanthines
4601	ASMABEC CLICKHALER dry powder inhaler 100micrograms [UCB]	beclometasone dipropionate	100micrograms	dry powder inhaler	Inhalation	Inhaled Corticosteroid
4634	STERI-NEB SALAMOL unit dose nebulising solution 2.5mg/2.5ml [IVAX]	salbutamol sulphate	2.5mg/2.5ml	unit dose nebulising solution	Nebulised	SABA
4640	BRICANYL unit dose nebuliser solution 5mg/2ml [ASTRAZENEC]	terbutaline sulphate	5mg/2ml	unit dose nebuliser solution	Nebulised	SABA
4647	INTAL SYNCRONER 5mg/inhalation [AVENTIS]	sodium cromoglicate	5mg/inhalation	SYNCRONER	Inhalation	Chromones
4657	cinchocaine with prednisolone ointment 5mg/g + 1.9mg/g	cinchocaine hydrochloride/prednisolone caproate	5mg/g + 1.9mg/g	ointment	Unknown	n/a
4665	SALBULIN cfc free inhaler 100micrograms/actuation [3M]	salbutamol sulphate	100micrograms / actuation	cfc free inhaler	Inhalation	SABA
4687	methylprednisolone acetate with lidocaine injection 40mg/ml + 10mg/ml	lidocaine hydrochloride/methylprednisolone acetate	40mg/ml + 10mg/ml	injection	Periarticular Injection	n/a

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
4688	fluticasone aerosol inhaler 50micrograms/actuation	fluticasone propionate	50micrograms/ actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
4759	beclometasone capsules (for inhalation) 100micrograms	beclometasone dipropionate	100micrograms	capsules (for inhalation)	Inhalation	Inhaled Corticosteroid
4801	budesonide nebuliser suspension 0.5mg/2ml	budesonide	0.5mg/2ml	nebuliser suspension	Nebulised	Inhaled Corticosteroid
4803	BECLAZONE aerosol inhaler 250micrograms/actuation [ACTAVIS]	beclometasone dipropionate	250micrograms / actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
4842	fenoterol aerosol inhaler 100micrograms/actuation	fenoterol hydrobromide	100micrograms / actuation	aerosol inhaler	Inhalation	SABA
4926	FLIXOTIDE ACCUHALER 100micrograms/inhalation [A & H]	fluticasone propionate	100micrograms / inhalation	ACCUHALER	Inhalation	Inhaled Corticosteroid
4942	budesonide nebuliser suspension 1mg/2ml	budesonide	1mg/2ml	nebuliser suspension	Nebulised	Inhaled Corticosteroid
5143	SERETIDE 50 EVOHALER cfc free inhaler 25micrograms + 50micrograms/actuation [A & H]	salmeterol xinafoate/fluticasone propionate	25micrograms + 50micrograms/ actuation	cfc free inhaler	Inhalation	Long acting beata agonist
5161	SERETIDE 125 EVOHALER cfc free inhaler 25micrograms + 125micrograms/actuation [A & H]	salmeterol xinafoate/fluticasone propionate	25micrograms + 125micrograms / actuation	cfc free inhaler	Inhalation	Long acting beata agonist
5170	SALAMOL cfc free inhaler 100micrograms/inhalation [IVAX]	salbutamol sulphate	100micrograms / inhalation	cfc free inhaler	Inhalation	SABA
5172	SERETIDE 250 EVOHALER cfc free inhaler 25micrograms + 250micrograms/actuation [A & H]	salmeterol xinafoate/fluticasone propionate	25micrograms + 250micrograms / actuation	cfc free inhaler	Inhalation	Long acting beata agonist
5185	fenoterol aerosol inhaler 200micrograms/actuation	fenoterol hydrobromide	200micrograms / actuation	aerosol inhaler	Inhalation	SABA
5223	fluticasone cfc free inhaler 50micrograms/actuation	fluticasone propionate	50micrograms/ actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
5261	NUELIN SA-250 tablets [MEDA]	theophylline		tablets	Oral	Xanthines
5308	terbutaline unit dose nebuliser solution 5mg/2ml	terbutaline sulphate	5mg/2ml	unit dose nebuliser solution	Nebulised	SABA
5309	FLIXOTIDE EVOHALER cfc free inhaler 50micrograms/actuation [A & H]	fluticasone propionate	50micrograms/ actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
5453	UNIPHYLLIN CONTINUS prolonged release tablet 400mg [NAPPPHARM]	theophylline	400mg	prolonged release tablet	Oral	Xanthines
5490	DELTACORTRIL ENTERIC tablets 5mg [ALLIANCE]	prednisolone	5mg	tablets	Oral	Prednisolone

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
5493	methylprednisolone acetate injection 40mg/ml	methylprednisolone acetate	40mg/ml	injection	Periarticular Injection	n/a
5516	SALAMOL EASI-BREATHE cfc free breath actuated inhaler 100micrograms/actuation [IVAX]	salbutamol sulphate	100micrograms / actuation	cfc free breath actuated inhaler	Inhalation	SABA
5521	beclometasone dry powder inhaler 200micrograms/actuation	beclometasone dipropionate	200micrograms / actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
5522	beclometasone dry powder inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
5551	FLIXOTIDE NEBULES unit dose nebulising suspension 500micrograms/2ml [A & H]	fluticasone propionate	500micrograms /2ml	unit dose nebulising suspension	Nebulised	Inhaled Corticosteroid
5558	salmeterol with fluticasone dry powder inhaler 50micrograms+ 500micrograms/inhalation	salmeterol xinafoate/fluticasone propionate	50micrograms+ 500micrograms /inhalation	dry powder inhaler	Inhalation	Long acting beata agonist
5580	FLIXOTIDE ACCUHALER 50micrograms/inhalation [A & H]	fluticasone propionate	50micrograms/ inhalation	ACCUHALER	Inhalation	Inhaled Corticosteroid
5594	SINGULAIR PAEDIATRIC chewable tablet 5mg [M S D]	montelukast sodium	5mg	chewable tablet	Oral	Leukotrienes
5683	FLIXOTIDE EVOHALER cfc free inhaler 250micrograms/actuation [A & H]	fluticasone propionate	250micrograms / actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
5718	FLIXOTIDE EVOHALER cfc free inhaler 125micrograms/actuation [A & H]	fluticasone propionate	125micrograms / actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
5740	AIROMIR AUTOHALER cfc free breath actuated inhaler 100micrograms/actuation [IVAX]	salbutamol sulphate	100micrograms / actuation	cfc free breath actuated inhaler	Inhalation	SABA
5753	salbutamol disc 400micrograms	salbutamol sulphate	400micrograms	disc	Inhalation	SABA
5804	beclometasone dry powder inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms / actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
5822	fluticasone cfc free inhaler 250micrograms/actuation	fluticasone propionate	250micrograms / actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
5837	SALAMOL STERI-NEB unit dose nebulising solution 5mg/2.5ml [NUMARK]	salbutamol sulphate	5mg/2.5ml	unit dose nebulising solution	Nebulised	SABA
5864	salmeterol with fluticasone cfc free inhaler 25micrograms + 250micrograms/actuation	salmeterol xinafoate/fluticasone propionate	25micrograms + 250micrograms / actuation	cfc free inhaler	Inhalation	Long acting beata agonist
5885	fluticasone dry powder inhaler 100micrograms/inhalation	fluticasone propionate	100micrograms /inhalation	dry powder inhaler	Inhalation	Inhaled Corticosteroid

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
5889	SALAMOL cfc free inhaler 100micrograms/inhalation [KENT]	salbutamol sulphate	100micrograms /inhalation	cfc free inhaler	Inhalation	SABA
5898	SALAMOL STERI-NEB unit dose nebulising solution 2.5mg/2.5ml [NUMARK]	salbutamol sulphate	2.5mg/2.5ml	unit dose nebulising solution	Nebulised	SABA
5913	DELTACORTRIL ENTERIC tablets 2.5mg [ALLIANCE]	prednisolone	2.5mg	tablets	Oral	Prednisolone
5941	UNIPHYLLIN CONTINUS prolonged release tablet 300mg [NAPPPHARM]	theophylline	300mg	prolonged release tablet	Oral	Xanthines
5942	salmeterol with fluticasone dry powder inhaler 50micrograms + 250micrograms/inhalation	salmeterol xinafoate/fluticasone propionate	50micrograms + 250micrograms /inhalation	dry powder inhaler	Inhalation	Long acting beata agonist
5957	montelukast (as sodium salt) chewable tablet 5mg	montelukast sodium	5mg	chewable tablet	Oral	Leukotrienes
5975	fluticasone cfc free inhaler 125micrograms/actuation	fluticasone propionate	125micrograms /actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
5992	beclometasone dry powder inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/ actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
6050	SPIRIVA capsules (for inhalation) 18 micrograms [BOEH INGL]	tiotropium bromide monohydrate	18 micrograms	capsules (for inhalation)	Inhalation	Antimuscarinic bronchodilator
6081	ipratropium bromide breath actuated inhaler 20micrograms/dose	ipratropium bromide	20micrograms/ dose	breath actuated inhaler	Inhalation	Antimuscarinic bronchodilator
6315	SLO-PHYLLIN capsules 250mg [MERCK SER]	theophylline	250mg	capsules	Oral	Xanthines
6325	SYMBICORT TURBOHALER dry powder inhaler 200micrograms + 6micrograms/actuation [ASTRAZENEC]	budesonide/formoterol fumarate dihydrate	200micrograms + 6micrograms/actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
6462	salbutamol dry powder inhaler 95micrograms	salbutamol sulphate	95micrograms	dry powder inhaler	Inhalation	SABA
6512	ATROVENT cfc free inhaler 20micrograms/actuation [BOEH INGL]	ipratropium bromide	20micrograms/ actuation	cfc free inhaler	Inhalation	Antimuscarinic bronchodilator
6522	ipratropium bromide cfc free inhaler 20micrograms/actuation	ipratropium bromide	20micrograms/ actuation	cfc free inhaler	Inhalation	Antimuscarinic bronchodilator
6526	formoterol fumarate capsules (for inhalation) 12mcg	formoterol fumarate	12mcg	capsules (for inhalation)	Inhalation	Long acting beata agonist
6569	salmeterol with fluticasone cfc free inhaler 25micrograms + 125micrograms/actuation	salmeterol xinafoate/fluticasone propionate	25micrograms + 125micrograms /actuation	cfc free inhaler	Inhalation	Long acting beata agonist

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
6616	salmeterol with fluticasone cfc free inhaler 25micrograms + 50micrograms/actuation	salmeterol xinafoate/fluticasone propionate	25micrograms + 50micrograms/ actuation	cfc free inhaler	Inhalation	Long acting beata agonist
6719	ipratropium bromide unit dose nebuliser solution 500micrograms/2ml	ipratropium bromide	500micrograms /2ml	unit dose nebuliser solution	Nebulised	Antimuscarinic bronchodilator
6746	budesonide with formoterol dry powder inhaler 400micrograms + 12micrograms/actuation	budesonide/formoterol fumarate dihydrate	400micrograms + 12micrograms/ actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
6758	STERI-NEB IPRATROPIUM unit dose nebulising solution 250micrograms/ml [IVAX]	ipratropium bromide	250micrograms /ml	unit dose nebulising solution	Nebulised	Antimuscarinic bronchodilator
6772	ipratropium bromide unit dose nebuliser solution 250micrograms/ml	ipratropium bromide	250micrograms /ml	unit dose nebuliser solution	Nebulised	Antimuscarinic bronchodilator
6780	SYMBICORT TURBOHALER dry powder inhaler 400micrograms + 12micrograms/actuation [ASTRAZENEC]	budesonide/formoterol fumarate dihydrate	400micrograms + 12micrograms/ actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
6796	budesonide with formoterol dry powder inhaler 200micrograms + 6micrograms/actuation	budesonide/formoterol fumarate dihydrate	200micrograms 6micrograms/actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
6839	ALVESCO cfc free inhaler 160micrograms/actuation [NYCOMED]	ciclesonide	160micrograms /actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
6911	ATROVENT UDVs nebuliser solution 250micrograms/1ml [BOEH INGL]	ipratropium bromide	250micrograms /1ml	nebuliser solution	Nebulised	Antimuscarinic bronchodilator
6938	salmeterol with fluticasone dry powder inhaler 50micrograms + 100micrograms/inhalation	salmeterol xinafoate/fluticasone propionate	50micrograms + 100micrograms /inhalation	dry powder inhaler	Inhalation	Long acting beata agonist
6988	aminophylline hydrate modified release tablet 100mg	aminophylline hydrate	100mg	modified release tablet	Oral	Xanthines
7013	SYMBICORT TURBOHALER dry powder inhaler 100micrograms + 6micrograms/actuation [ASTRAZENEC]	budesonide/formoterol fumarate dihydrate	100micrograms + 6micrograms/actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
7017	salbutamol dry powder inhaler 100micrograms/actuation	salbutamol sulphate	100micrograms /actuation	dry powder inhaler	Inhalation	SABA
7088	montelukast (as sodium salt) granules 4mg/sachet	montelukast sodium	4mg/sachet	granules	Oral	Leukotrienes

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
7132	zafirlukast tablets 20mg	zafirlukast	20mg	tablets	Oral	Leukotrienes
7133	formoterol fumarate dry powder inhaler 12micrograms/actuation	formoterol fumarate dihydrate	12micrograms/ actuation	dry powder inhaler	Inhalation	Long acting beata agonist
7140	ATROVENT UDVs nebuliser solution 500micrograms/2ml [BOEH INGL]	ipratropium bromide	500micrograms /2ml	nebuliser solution	Nebulised	Antimuscarinic bronchodilator
7192	bambuterol tablets 10mg	bambuterol hydrochloride	10mg	tablets	Oral	Long acting beata agonist
7268	SEREVENT EVOHALER cfc free inhaler 25micrograms/actuation [GLAXO]	salmeterol xinafoate	25micrograms/ actuation	cfc free inhaler	Inhalation	Long acting beata agonist
7270	salmeterol cfc free inhaler 25micrograms/actuation	salmeterol xinafoate	25micrograms/ actuation	cfc free inhaler	Inhalation	Long acting beata agonist
7356	ciclesonide cfc free inhaler 80micrograms/actuation	ciclesonide	80micrograms/ actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
7405	DEPO-MEDRONE WITH LIDOCAINE injection 40mg/1ml + 10mg/1ml [PHARMACIA]	lidocaine hydrochloride/methylprednisolone acetate	40mg/1ml + 10mg/1ml	injection	Tendon sheath injection	n/a
7477	FRANOL PLUS tablets [SANOFI S]	ephedrine sulphate/theophylline		tablets	Oral	Adrenreceptor Agonist
7550	omalizumab injection 150mg	omalizumab	150mg	injection	Subcutaneous Injection	Anti IgE agents
7602	fluticasone disc 50micrograms	fluticasone propionate	50micrograms	disc	Inhalation	Inhaled Corticosteroid
7638	fluticasone disc 250micrograms	fluticasone propionate	250micrograms	disc	Inhalation	Inhaled Corticosteroid
7653	beclometasone capsules (for inhalation) 400micrograms	beclometasone dipropionate	400micrograms	capsules (for inhalation)	Inhalation	Inhaled Corticosteroid
7711	terbutaline spacer inhaler 250micrograms/actuation	terbutaline sulphate	250micrograms /actuation	spacer inhaler	Inhalation	SABA
7719	ephedrine tablets 30mg	ephedrine hydrochloride	30mg	tablets	Oral	Adrenreceptor Agonist
7730	THEO-DUR tablets 300mg [ASTRAZENEC]	theophylline	300mg	tablets	Oral	Xanthines
7731	THEO-DUR tablets 200mg [ASTRAZENEC]	theophylline	200mg	tablets	Oral	Xanthines
7732	theophylline modified release tablet 300mg	theophylline	300mg	modified release tablet	Oral	Xanthines
7733	theophylline modified release tablet 250mg	theophylline	250mg	modified release tablet	Oral	Xanthines
7788	budesonide dry powder inhaler 100micrograms/actuation	budesonide	100micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
7841	NUELIN tablets 125mg [3M]	theophylline	125mg	tablets	Oral	Xanthines

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
7891	fluticasone disc 500micrograms	fluticasone propionate	500micrograms	disc	Inhalation	Inhaled Corticosteroid
7935	MAXIVENT aerosol inhaler 100micrograms/inhalation [ASHBOURNE]	salbutamol sulphate	100micrograms /inhalation	aerosol inhaler	Inhalation	SABA
7948	fluticasone dry powder inhaler 250micrograms/inhalation	fluticasone propionate	250micrograms /inhalation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
7953	terbutaline sugar free oral solution 1.5mg/5ml	terbutaline sulphate	1.5mg/5ml	sugar free oral solution	Oral	SABA
7954	BRICANYL spacer inhaler [ASTRAZENEC]	terbutaline sulphate		spacer inhaler	Inhalation	SABA
7964	beclometasone nebuliser suspension 50micrograms/ml	beclometasone dipropionate	50micrograms/ ml	nebuliser suspension	Nebulised	Inhaled Corticosteroid
7965	salbutamol respirator solution 5mg/ml	salbutamol sulphate	5mg/ml	respirator solution	Nebulised	SABA
7972	INTAL FISONAIR aerosol inhaler 5mg/inhalation [AVENTIS]	sodium cromoglicate	5mg/inhalation	aerosol inhaler	Inhalation	Chromones
8056	aminophylline tablets 100mg	aminophylline	100mg	tablets	Oral	Xanthines
8057	aminophylline modified release tablet 100mg	aminophylline hydrate	100mg	modified release tablet	Oral	Xanthines
8111	BECLOFORTE VM pack 250micrograms/actuation [A & H]	beclometasone dipropionate	250micrograms /actuation	VM pack	Inhalation	Inhaled Corticosteroid
8215	TILADE aerosol inhaler 2mg/inhalation [SANOFI/AVE]	nedocromil sodium	2mg/inhalation	aerosol inhaler	Inhalation	Chromones
8267	sodium cromoglicate with salbutamol aerosol inhaler	salbutamol/sodium cromoglicate		aerosol inhaler	Inhalation	SABA
8306	prednisolone acetate injection 25mg/ml	prednisolone acetate	25mg/ml	injection	Periarticular Injection	Prednisolone
8333	ipratropium bromide capsules (for inhalation) 40mcg	ipratropium bromide	40mcg	capsules (for inhalation)	Inhalation	Antimuscarinic bronchodilator
8433	budesonide aerosol inhaler 100micrograms/actuation	budesonide	100micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
8498	sodium cromoglicate nebuliser solution 10mg/ml	sodium cromoglicate	10mg/ml	nebuliser solution	Nebulised	Chromones
8511	CAM sugar free liquid 4mg/5ml [CAMBHEALTH]	ephedrine hydrochloride	4mg/5ml	sugar free liquid	Oral	Adrenreceptor Agonist
8522	terbutaline modified release tablet 7.5mg	terbutaline sulphate	7.5mg	modified release tablet	Oral	SABA
8608	nedocromil sodium aerosol inhaler 2mg/inhalation	nedocromil sodium	2mg/inhalation	aerosol inhaler	Inhalation	Chromones
8635	FLIXOTIDE disc 50micrograms [A & H]	fluticasone propionate	50micrograms	disc	Inhalation	Inhaled Corticosteroid
8676	terbutaline respirator solution 10mg/ml	terbutaline sulphate	10mg/ml	respirator solution	Nebulised	SABA
8806	PHYLLOCONTIN CONTINUS forte tablets 350mg [NAPPPHARM]	aminophylline hydrate	350mg	forte tablets	Oral	Xanthines

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
9092	theophylline modified release tablet 350mg	theophylline	350mg	modified release tablet	Oral	Xanthines
9164	fluticasone dry powder inhaler 50micrograms/inhalation	fluticasone propionate	50micrograms/inhalation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
9233	beclometasone capsules (for inhalation) 200micrograms	beclometasone dipropionate	200micrograms	capsules (for inhalation)	Inhalation	Inhaled Corticosteroid
9270	ipratropium bromide with fenoterol hydrobromide unit dose nebulising solution 500micrograms + 1.25mg/4ml	fenoterol hydrobromide/ipratropium bromide	500micrograms + 1.25mg/4ml	unit dose nebulising solution	Nebulised	SABA
9384	salbutamol modified release capsules 4mg	salbutamol sulphate	4mg	modified release capsules	Oral	SABA
9477	ASMABEC SPACEHALER 100micrograms/actuation [CELLTECH]	beclometasone dipropionate	100micrograms/actuation	SPACEHALER	Inhalation	Inhaled Corticosteroid
9571	beclometasone vortex metered dose inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms/actuation	vortex metered dose inhaler	Inhalation	Inhaled Corticosteroid
9577	ASMABEC CLICKHALER dry powder inhaler 50micrograms [UCB]	beclometasone dipropionate	50micrograms	dry powder inhaler	Inhalation	Inhaled Corticosteroid
9599	BECLAZONE aerosol inhaler 50micrograms/actuation [ACTAVIS]	beclometasone dipropionate	50micrograms/actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
9635	ZADITEN sugar free elixir 1mg/5ml [NOV/SANDOZ]	ketotifen hydrogen fumarate	1mg/5ml	sugar free elixir	Oral	anti histamine
9651	ASMASAL SPACEHALER 100micrograms/inhalation [CELLTECH]	salbutamol	100micrograms/inhalation	SPACEHALER	Inhalation	SABA
9681	ATROVENT AEROHALER 40mcg [BOEH INGL]	ipratropium bromide	40mcg	AEROHALER	Inhalation	Antimuscarinic bronchodilator
9706	ephedrine elixir 15mg/5ml	ephedrine hydrochloride	15mg/5ml	elixir	Oral	Adrenreceptor Agonist
9711	formoterol fumarate dry powder inhaler 6 micrograms/actuation	formoterol fumarate dihydrate	6 micrograms/actuation	dry powder inhaler	Inhalation	Long acting beata agonist
9720	ephedrine hydrochloride elixir 15mg/5ml	ephedrine hydrochloride	15mg/5ml	elixir	Oral	Adrenreceptor Agonist
9727	prednisolone tablets 50mg	prednisolone	50mg	tablets	Oral	Prednisolone
9805	salbutamol infusion 100micrograms/ml	salbutamol sulphate	100micrograms/ml	infusion	Unknown	SABA
9813	DIMOTANE PLUS PAEDIATRIC sugar free elixir [GOLDSHIELD]	brompheniramine maleate/pseudoephedrine hydrochloride		sugar free elixir	Oral	Adrenreceptor Agonist
9818	DIMOTANE PLUS sugar free elixir [GOLDSHIELD]	brompheniramine maleate/pseudoephedrine		sugar free elixir	Oral	Adrenreceptor Agonist

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
		hydrochloride				
9921	beclometasone extra fine particle cfc free breath actuated inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms /actuation	cfc free breath actuated inhaler	Inhalation	Inhaled Corticosteroid
10090	beclometasone extra fine particle cfc free inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/ actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
10102	ciclesonide cfc free inhaler 160micrograms/actuation	ciclesonide	160micrograms /actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
10218	budesonide with formoterol dry powder inhaler 100micrograms + 6micrograms/actuation	budesonide/formoterol fumarate dihydrate	100micrograms +6micrograms/ actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
10254	mometasone furoate dry powder inhaler 400micrograms/actuation	mometasone furoate	400micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
10297	BENYLIN DECONGESTANT syrup [WARN/LAMB]	diphenhydramine hydrochloride/ menthol/pseudoephedrine hydrochloride/sodium citrate		syrup	Oral	Adrenreceptor Agonist
10321	budesonide capsules (for inhalation) 400micrograms	budesonide	400micrograms	capsules (for inhalation)	Inhalation	Inhaled Corticosteroid
10331	NUELIN liquid 60mg/5ml [3M]	theophylline sodium glycinate	60mg/5ml	liquid	Oral	Xanthines
10360	AEROCROM aerosol inhaler [CASTLEMEAD]	salbutamol/sodium cromoglicate		aerosol inhaler	Inhalation	SABA
10407	PHYLLOCONTIN CONTINUS pediatric tablets 100mg [NAPPPHARM]	aminophylline hydrate	100mg	pediatric tablets	Oral	Xanthines
10433	theophylline liquid 60mg/5ml	theophylline sodium glycinate	60mg/5ml	liquid	Oral	Xanthines
10458	VENTOLIN CR tablets 4mg [A & H]	salbutamol sulphate	4mg	tablets	Oral	SABA
10561	aminophylline injection 250mg/ml	aminophylline	250mg/ml	injection	Unknown	Xanthines
10597	TILADE mint SYNCRONER 2mg/inhalation [SANOFI/AVE]	nedocromil sodium	2mg/inhalation	mint SYNCRONER	Inhalation	Chromones
10723	theophylline syrup 125mg/5ml	theophylline sodium glycinate	125mg/5ml	syrup	Oral	Xanthines
10812	ZADITEN capsules 1mg [NOV/SANDOZ]	ketotifen hydrogen fumarate	1mg	capsules	Oral	anti histamine
10813	ketotifen capsules 1mg	ketotifen hydrogen fumarate	1mg	capsules	Oral	anti histamine
10825	terbutaline tablets 5mg	terbutaline sulphate	5mg	tablets	Oral	SABA
10831	BIOPHYLLINE syrup 125mg/5ml [LOREX]	theophylline sodium glycinate	125mg/5ml	syrup	Oral	Xanthines
10968	FORADIL capsules (for inhalation) 12mcg [NOV/CIBA]	formoterol fumarate	12mcg	capsules (for inhalation)	Inhalation	Long acting beata agonist
10979	ephedrine tablets 15mg	ephedrine hydrochloride	15mg	tablets	Oral	Adrenreceptor Agonist
11046	ipratropium bromide with salbutamol unit dose nebulising	ipratropium	500micrograms	unit dose	Nebulised	Antimuscarinic

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
	solution 500micrograms + 2.5mg/2.5ml	bromide/salbutamol sulphate	+ 2.5mg/2.5ml	nebulising solution		bronchodilator
11198	beclometasone vortex metered dose inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/ actuation	vortex metered dose inhaler	Inhalation	Inhaled Corticosteroid
11307	salbutamol with beclometasone aerosol inhaler 100mcg + 50mcg	beclometasone dipropionate/salbutamol	100mcg + 50mcg	aerosol inhaler	Inhalation	Inhaled Corticosteroid
11410	fluticasone with salmeterol dry powder inhaler 500micrograms + 50micrograms/inhalation	salmeterol xinafoate/fluticasone propionate	500micrograms +50micrograms /inhalation	dry powder inhaler	Unknown	Long acting beata agonist
11478	fluticasone unit dose nebulising suspension 2mg/2ml	fluticasone propionate	2mg/2ml	unit dose nebulising suspension	Nebulised	Inhaled Corticosteroid
11497	beclometasone dry powder inhaler 400micrograms/actuation	beclometasone dipropionate	400micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
11588	fluticasone with salmeterol cfc free inhaler 125micrograms + 25micrograms/actuation	salmeterol xinafoate/fluticasone propionate	125micrograms +25micrograms /actuation	cfc free inhaler	Unknown	Long acting beata agonist
11618	fluticasone with salmeterol cfc free inhaler 250micrograms + 25micrograms/actuation	salmeterol xinafoate/fluticasone propionate	250micrograms +25micrograms /actuation	cfc free inhaler	Unknown	Long acting beata agonist
11719	SLO-PHYLLIN capsules 60mg [MERCK SER]	theophylline	60mg	capsules	Oral	Xanthines
11732	beclometasone extra fine particle cfc free breath actuated inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/ actuation	cfc free breath actuated inhaler	Inhalation	Inhaled Corticosteroid
11779	ipratropium bromide capsules for inhalation + inhaler 40mcg	ipratropium bromide	40mcg	capsules for inhalation + inhaler	Inhalation	Antimuscarinic bronchodilator
11993	PRO-VENT capsules 300mg [WELLCOME]	theophylline	300mg	capsules	Oral	Xanthines
12042	VENTOLIN CR tablets 8mg [A & H]	salbutamol sulphate	8mg	tablets	Oral	SABA
12144	bambuterol tablets 20mg	bambuterol hydrochloride	20mg	tablets	Oral	Long acting beata agonist
12240	theophylline modified release capsules 300mg	theophylline	300mg	modified release capsules	Oral	Xanthines
12274	TEDRAL tablets [PARKE]	ephedrine hydrochloride/theophylline		tablets	Oral	Adrenreceptor Agonist
12405	methylprednisolone sodium succ injection 2g	methylprednisolone sodium succinate	2g	injection	Intravenous Injection	n/a

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
12699	PECRAM sustained release tablets 225mg [NOVARTIS]	aminophylline hydrate	225mg	sustained release tablets	Oral	Xanthines
12808	fenoterol with ipratropium bromide breath actuated inhaler 100micrograms + 40micrograms/actuation	fenoterol hydrobromide/ipratropium bromide	100micrograms +40micrograms /actuation	breath actuated inhaler	Inhalation	SABA
12822	salbutamol with ipratropium bromide unit dose nebulising solution 2.5mg + 500micrograms/2.5ml	ipratropium bromide/salbutamol sulphate	2.5mg +500micrograms /2.5ml	unit dose nebulising solution	Unknown	Antimuscarinic bronchodilator
12909	salbutamol with ipratropium bromide aerosol inhaler 100micrograms + 20micrograms/actuation	ipratropium bromide/salbutamol sulphate	100micrograms +20micrograms /actuation	aerosol inhaler	Unknown	Antimuscarinic bronchodilator
12994	fluticasone with salmeterol cfc free inhaler 50micrograms + 25micrograms/actuation	salmeterol xinafoate/fluticasone propionate	50micrograms + 25micrograms/ actuation	cfc free inhaler	Unknown	Long acting beata agonist
13037	PULVINAL BECLOMETASONE DIPROPIONATE dry powder inhaler 200micrograms/actuation [CHIESI]	beclometasone dipropionate	200micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
13038	PULVINAL SALBUTAMOL dry powder inhaler 200micrograms/actuation [CHIESI]	salbutamol sulphate	200micrograms /actuation	dry powder inhaler	Inhalation	SABA
13040	fluticasone with salmeterol dry powder inhaler 250micrograms + 50micrograms/inhalation	salmeterol xinafoate/fluticasone propionate	250micrograms +50micrograms /inhalation	dry powder inhaler	Unknown	Long acting beata agonist
13181	EASYHALER SALBUTAMOL dry powder inhaler 100micrograms/actuation [ORION]	salbutamol sulphate	100micrograms /actuation	dry powder inhaler	Inhalation	SABA
13256	nedocromil sodium cfc free inhaler 2mg/inhalation	nedocromil sodium	2mg/inhalation	cfc free inhaler	Inhalation	Chromones
13273	fluticasone with salmeterol dry powder inhaler 100micrograms + 50micrograms/inhalation	salmeterol xinafoate/fluticasone propionate	100micrograms +50micrograms /inhalation	dry powder inhaler	Unknown	Long acting beata agonist
13290	CLENIL MODULITE cfc free inhaler 100micrograms/actuation [CHIESI]	beclometasone dipropionate	100micrograms /actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
13307	BRICANYL injection 500micrograms/ml [ASTRAZENEC]	terbutaline sulphate	500micrograms /ml	injection	Subcutaneous Injection	SABA
13365	BEROTEC nebuliser solution 5mg/ml [BOEH INGL]	fenoterol hydrobromide	5mg/ml	nebuliser solution	Nebulised	SABA
13397	methylprednisolone sodium succ injection 1g	methylprednisolone sodium succinate	1g	injection	Intravenous Injection	n/a
13529	AMNIVENT sustained release tablets 225mg [ASHBOURNE]	aminophylline hydrate	225mg	sustained release tablets	Oral	Xanthines
13575	BAMBEC tablets 20mg [ASTRAZENEC]	bambuterol hydrochloride	20mg	tablets	Oral	Long acting beata

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
						agonist
13757	TROPIOVENT STERIPOULE unit dose nebulising solution 250micrograms/ml [ASHBOURNE]	ipratropium bromide	250micrograms /ml	unit dose nebulising solution	Nebulised	Antimuscarinic bronchodilator
13815	BECLAZONE aerosol inhaler 100micrograms/actuation [ACTAVIS]	beclometasone dipropionate	100micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
13996	SALAMOL cfc free inhaler 100micrograms/inhalation [SANDOZ]	salbutamol sulphate	100micrograms /inhalation	cfc free inhaler	Inhalation	SABA
14162	SINGULAIR PAEDIATRIC chewable tablet 4mg [M S D]	montelukast sodium	4mg	chewable tablet	Oral	Leukotrienes
14188	methylprednisolone sodium succ injection 500mg	methylprednisolone sodium succinate	500mg	injection	Intravenous Injection	n/a
14200	SINGULAIR PAEDIATRIC granules 4mg/sachet [M S D]	montelukast sodium	4mg/sachet	granules	Oral	Leukotrienes
14294	QVAR EASI-BREATHE cfc free breath actuated inhaler 50micrograms/actuation [IVAX]	beclometasone dipropionate	50micrograms/ actuation	cfc free breath actuated inhaler	Inhalation	Inhaled Corticosteroid
14306	formoterol fumarate cfc free inhaler 12micrograms/actuation	formoterol fumarate dihydrate	12micrograms/ actuation	cfc free inhaler	Inhalation	Long acting beata agonist
14321	beclometasone cfc free inhaler 200micrograms/actuation	beclometasone dipropionate	200micrograms /actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
14382	ephedrine hydrochloride tablets 15mg	ephedrine hydrochloride	15mg	tablets	Oral	Adrenreceptor Agonist
14472	magnesium sulphate injection 50%	magnesium sulphate	50%	injection	Intravenous Injection	Magnesium sulphate
14483	terbutaline injection 500micrograms/ml	terbutaline sulphate	500micrograms /ml	injection	Subcutaneo us Injection	SABA
14524	BDP SPACEHALER 250micrograms/actuation [CELLTECH]	beclometasone dipropionate	250micrograms /actuation	SPACEHALER	Inhalation	Inhaled Corticosteroid
14525	salbutamol vortex metered dose inhaler 100micrograms/inhalation	salbutamol	100micrograms /inhalation	vortex metered dose inhaler	Inhalation	SABA
14527	BAMBEC tablets 10mg [ASTRAZENEC]	bambuterol hydrochloride	10mg	tablets	Oral	Long acting beata agonist
14561	salbutamol with beclometasone capsules (for inhalation) 400micrograms + 200micrograms	beclometasone dipropionate/salbutamol	400micrograms +200microgram	capsules (for inhalation)	Inhalation	Inhaled Corticosteroid
14567	ASMABEC CLICKHALER dry powder inhaler 250micrograms [UCB]	beclometasone dipropionate	250micrograms	dry powder inhaler	Inhalation	Inhaled Corticosteroid
14590	ASMABEC SPACEHALER 250micrograms/actuation [CELLTECH]	beclometasone dipropionate	250micrograms /actuation	SPACEHALER	Inhalation	Inhaled Corticosteroid
14603	sodium cromoglicate inhaler and spacer 5mg/actuation	sodium cromoglicate	5mg/actuation	inhaler and	Inhalation	Chromones

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
				spacer		
14700	budesonide aerosol inhaler 400micrograms/actuation	budesonide	400micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
14736	PULVINAL BECLOMETASONE DIPROPIONATE dry powder inhaler 400micrograms/actuation [CHIESI]	beclometasone dipropionate	400micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
14739	NORPHYLLIN SR tablets 225mg [IVAX]	aminophylline hydrate	225mg	tablets	Oral	Xanthines
14757	PULVINAL BECLOMETASONE DIPROPIONATE dry powder inhaler 100micrograms/actuation [CHIESI]	beclometasone dipropionate	100micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
14982	DEPO-MEDRONE injection 40mg/1ml [PHARMACIA]	methylprednisolone acetate	40mg/1ml	injection	Tendon sheath injection	n/a
14991	aminophylline injection 250mg/10ml	aminophylline	250mg/10ml	injection	Intravenous Injection	Xanthines
15153	theophylline with ephedrine hydrochloride tablets 120mg + 11mg	ephedrine hydrochloride/theophylline	120mg + 11mg	tablets	Oral	Adrenreceptor Agonist
15284	SLO-PHYLLIN capsules 125mg [MERCK SER]	theophylline	125mg	capsules	Oral	Xanthines
15326	beclometasone cfc free inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms /actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
15356	EPHEDRINE HYDROCHLORIDE tablets 30mg [CP PHARM]	ephedrine hydrochloride	30mg	tablets	Oral	Adrenreceptor Agonist
15365	theophylline sugar free elixir 10mg/5ml	theophylline sodium glycinate	10mg/5ml	sugar free elixir	Oral	Xanthines
15467	ephedrine tablets 60mg	ephedrine hydrochloride	60mg	tablets	Oral	Adrenreceptor Agonist
15483	BRICANYL expectorant [ASTRAZENEC]	guaifenesin/terbutaline sulphate		expectorant	Oral	n/a
15613	salbutamol injection 500micrograms/1ml	salbutamol sulphate	500micrograms /1ml	injection	Subcutaneous Injection	SABA
15706	beclometasone vortex metered dose inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms /actuation	vortex metered dose inhaler	Inhalation	Inhaled Corticosteroid
15765	sodium cromoglicate inhaler and spacer 5mg/inhalation	sodium cromoglicate	5mg/inhalation	inhaler and spacer	Inhalation	Chromones
15816	ephedrine hydrochloride tablets 30mg	ephedrine hydrochloride	30mg	tablets	Oral	Adrenreceptor Agonist
16018	mometasone furoate dry powder inhaler 200micrograms/actuation	mometasone furoate	200micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
16054	budesonide refillable breath actuated dry powder inhaler 200micrograms/actuation	budesonide	200micrograms /actuation	breath actuated dry powder inhaler	Inhalation	Inhaled Corticosteroid
16148	CLENIL MODULITE cfc free inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms	cfc free inhaler	Inhalation	Inhaled Corticosteroid

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
	[CHIESI]		/actuation			
16151	CLENIL MODULITE cfc free inhaler 200micrograms/actuation [CHIESI]	beclometasone dipropionate	200micrograms /actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
16158	CLENIL MODULITE cfc free inhaler 50micrograms/actuation [CHIESI]	beclometasone dipropionate	50micrograms/ actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
16207	DUOVENT UDVs nebuliser solution [BOEH INGL]	fenoterol hydrobromide/ ipratropium bromide		nebuliser solution	Nebulised	SABA
16305	FLIXOTIDE NEBULES unit dose nebulising suspension 2mg/2ml [A & H]	fluticasone propionate	2mg/2ml	unit dose nebulising suspension	Nebulised	Inhaled Corticosteroid
16433	ASMANEX TWISTHALER dry powder inhaler 200micrograms/actuation [SCHERING-P]	mometasone furoate	200micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
16525	BUDENOFALK capsules 3mg [DR FALK]	budesonide	3mg	capsules	Oral	Inhaled Corticosteroid
16577	EASYHALER SALBUTAMOL dry powder inhaler 200micrograms/actuation [ORION]	salbutamol sulphate	200micrograms /actuation	dry powder inhaler	Inhalation	SABA
16584	beclometasone cfc free inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/ actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
16625	VENTIDE ROTACAPS [A & H]	beclometasone dipropionate/salbutamol		ROTACAPS	Inhalation	Inhaled Corticosteroid
16994	aminophylline hydrate modified release tablet 350mg	aminophylline hydrate	350mg	modified release tablet	Oral	Xanthines
17002	aminophylline hydrate modified release tablet 225mg	aminophylline hydrate	225mg	modified release tablet	Oral	Xanthines
17140	aminophylline tablets 200mg	aminophylline	200mg	tablets	Oral	Xanthines
17185	VENTOLIN injection 500micrograms/1ml [A & H]	salbutamol sulphate	500micrograms /1ml	injection	Subcutaneo us Injection	SABA
17465	fluticasone unit dose nebulising suspension 500micrograms/2ml	fluticasone propionate	500micrograms /2ml	unit dose nebulising suspension	Nebulised	Inhaled Corticosteroid
17562	diphenhydramine with pseudoephedrine hydrochloride syrup	diphenhydramine hydrochloride/ pseudoephedrine hydrochloride		syrup	Oral	Adrenreceptor Agonist
17590	ASMANEX TWISTHALER dry powder inhaler 400micrograms/actuation [SCHERING-P]	mometasone furoate	400micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
17654	EASYHALER BECLOMETASONE dry powder inhaler	beclometasone dipropionate	200micrograms	dry powder	Inhalation	Inhaled Corticosteroid

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
	200micrograms/actuation [ORION]		/actuation	inhaler		
17670	EASYHALER BUDESONIDE dry powder inhaler 100micrograms/actuation [ORION]	budesonide	100micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
17696	VENTMAX SR modified release capsules 4mg [OPUS]	salbutamol sulphate	4mg	modified release capsules	Oral	SABA
17874	MONOVENT syrup 1.5mg/5ml [LAGAP]	terbutaline sulphate	1.5mg/5ml	syrup	Oral	SABA
17875	terbutaline with guaifenesin expectorant	guaifenesin/terbutaline sulphate		expectorant	Oral	n/a
18140	RESPONTIN NEBULES unit dose nebulising solution 500micrograms/2ml [GLAXO]	ipratropium bromide	500micrograms /2ml	unit dose nebulising solution	Nebulised	Antimuscarinic bronchodilator
18266	methylprednisolone sodium succ injection 125mg	methylprednisolone sodium succinate	125mg	injection	Intravenous Injection	n/a
18299	fenoterol with ipratropium bromide unit dose nebulising solution 1.25mg + 500micrograms/4ml	fenoterol hydrobromide/ ipratropium bromide	1.25mg + 500mcg/4ml	unit dose nebulising solution	Unknown	SABA
18314	AEROCROM SYNCRONER [CASTLEMEAD]	salbutamol/sodium cromoglicate		SYNCRONER	Inhalation	SABA
18394	BDP SPACEHALER 50micrograms/actuation [CELLTECH]	beclometasone dipropionate	50micrograms/ actuation	SPACEHALER	Inhalation	Inhaled Corticosteroid
18421	RESPONTIN NEBULES unit dose nebulising solution 250micrograms/ml [GLAXO]	ipratropium bromide	250micrograms /ml	unit dose nebulising solution	Nebulised	Antimuscarinic bronchodilator
18456	salbutamol with beclometasone capsules (for inhalation) 200micrograms + 100micrograms	beclometasone dipropionate/salbutamol	200micrograms +100microgram	capsules (for inhalation)	Inhalation	Inhaled Corticosteroid
18484	VENTIDE pediatric ROTACAPS [A & H]	beclometasone dipropionate/salbutamol		pediatric ROTACAPS	Inhalation	Inhaled Corticosteroid
18537	budesonide capsules (for inhalation) 200micrograms	budesonide	200micrograms	capsules (for inhalation)	Inhalation	Inhaled Corticosteroid
18622	SALBULIN tablets 2mg [3M]	salbutamol sulphate	2mg	tablets	Oral	SABA
18660	DELTASTAB injection 25mg/ml [SOVEREIGN]	prednisolone acetate	25mg/ml	injection	Periarticular Injection	Prednisolone
18765	methylprednisolone sodium succ injection 40mg	methylprednisolone sodium succinate	40mg	injection	Intravenous Injection	n/a
18848	QVAR EASI-BREATHE cfc free breath actuated inhaler 100micrograms/actuation [IVAX]	beclometasone dipropionate	100micrograms /actuation	cfc free breath actuated inhaler	Inhalation	Inhaled Corticosteroid

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
18968	salbutamol concentrate for solution for infusion 5mg/5ml	salbutamol sulphate	5mg/5ml	concentrate for solution for infusion	Intravenous Infusion	SABA
19031	BDP SPACEHALER 100micrograms/actuation [CELLTECH]	beclometasone dipropionate	100micrograms /actuation	SPACEHALER	Inhalation	Inhaled Corticosteroid
19121	beclometasone with salbutamol capsules (for inhalation) 100micrograms + 200micrograms	beclometasone dipropionate/salbutamol	100micrograms +200micrograms	capsules (for inhalation)	Unknown	Inhaled Corticosteroid
19141	PREDNISOLONE soluble tablet 5mg [SOVEREIGN]	prednisolone sodium phosphate	5mg	soluble tablet	Oral	Prednisolone
19376	beclometasone with salbutamol capsules (for inhalation) 200micrograms + 400micrograms	beclometasone dipropionate/salbutamol	200micrograms +400micrograms	capsules (for inhalation)	Unknown	Inhaled Corticosteroid
19389	ASMABEC SPACEHALER 50micrograms/actuation [CELLTECH]	beclometasone dipropionate	50micrograms/ actuation	SPACEHALER	Inhalation	Inhaled Corticosteroid
19401	beclometasone inhaler with compact spacer 250micrograms/actuation	beclometasone dipropionate	250micrograms /actuation	inhaler with compact spacer	Inhalation	Inhaled Corticosteroid
19917	pseudoephedrine with paracetamol tablets 60mg + 500mg	paracetamol/pseudoephedrine hydrochloride	60mg + 500mg	tablets	Oral	Adrenreceptor Agonist
19953	theophylline with ephedrine and caffeine tablets	caffeine/ephedrine/theophylline		tablets	Oral	Adrenreceptor Agonist
20095	PRECORTISYL FORTE tablets 25mg [AVENTIS]	prednisolone	25mg	tablets	Oral	Prednisolone
20180	sodium cromoglicate with isoprenaline capsules (for inhalation)	isoprenaline sulphate/sodium cromoglicate		capsules (for inhalation)	Inhalation	Chromones
20825	SPACEHALER BDP SPACEHALER 250micrograms/actuation [CELLTECH]	beclometasone dipropionate	250micrograms /actuation	SPACEHALER	Inhalation	Inhaled Corticosteroid
20838	SALBUVENT tablets 2mg [PHARMACIA]	salbutamol sulphate	2mg	tablets	Oral	SABA
21005	beclometasone cfc free inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms /actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
21102	SALBUTAMOL sugar free syrup 2mg/5ml [LAGAP]	salbutamol sulphate	2mg/5ml	sugar free syrup	Oral	SABA
21224	ALVESCO cfc free inhaler 80micrograms/actuation [NYCOMED]	ciclesonide	80micrograms/ actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
21417	PREDNISOLONE tablets 5mg [HILLCROSS]	prednisolone	5mg	tablets	Oral	Prednisolone
21482	BECLOMETASONE aerosol inhaler 100micrograms/actuation [GEN (UK)]	beclometasone dipropionate	100micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
21540	SOLU-MEDRONE injection 500mg [PHARMACIA]	methylprednisolone sodium	500mg	injection	Intravenous	n/a

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
		succinate			Injection	
21769	LASMA tablets 300mg [PHARMAX]	theophylline	300mg	tablets	Oral	Xanthines
21859	ASMAVEN aerosol inhaler 100micrograms [BERK]	salbutamol sulphate	100micrograms	aerosol inhaler	Inhalation	SABA
22313	VENTMAX SR modified release capsules 8mg [OPUS]	salbutamol sulphate	8mg	modified release capsules	Oral	SABA
22330	ephedrine hydrochloride sugar free liquid 4mg/5ml	ephedrine hydrochloride	4mg/5ml	sugar free liquid	Oral	Adrenreceptor Agonist
22430	SPACEHALER SALBUTAMOL SPACEHALER 100micrograms/inhalation [CELLTECH]	salbutamol	100micrograms /inhalation	SPACEHALER	Inhalation	SABA
23047	ephedrine hydrochloride tablets 60mg	ephedrine hydrochloride	60mg	tablets	Oral	Adrenreceptor Agonist
23269	MAXIVENT STERIPOULE unit dose nebulising solution 2.5mg/2.5ml [ASHBOURNE]	salbutamol sulphate	2.5mg/2.5ml	unit dose nebulising solution	Nebulised	SABA
23511	SOLU-MEDRONE injection 40mg [PHARMACIA]	methylprednisolone sodium succinate	40mg	injection	Intravenous Injection	n/a
23512	PRECORTISYL tablets 5mg [HOECHSTMAR]	prednisolone	5mg	tablets	Oral	Prednisolone
23567	RESPONTIN NEBULES unit dose nebulising solution 250micrograms/ml [GLAXO]	ipratropium bromide	250micrograms /ml	unit dose nebulising solution	Nebulised	Antimuscarinic bronchodilator
23572	AMINOPHYLLINE SR tablets 225mg [IVAX]	aminophylline hydrate	225mg	SR tablets	Oral	Xanthines
23709	STERI-NEB IPRATROPIUM unit dose nebulising solution 500micrograms/2ml [IVAX]	ipratropium bromide	500micrograms /2ml	unit dose nebulising solution	Nebulised	Antimuscarinic bronchodilator
23741	NOVOLIZER BUDESONIDE breath actuated dry powder inhaler 200micrograms/actuation [MEDA]	budesonide	200micrograms /actuation	breath actuated dry powder inhaler	Inhalation	Inhaled Corticosteroid
23961	IPRATROPIUM BROMIDE inhalation solution 250micrograms/ml [GALEN]	ipratropium bromide	250micrograms /ml	inhalation solution	Nebulised	Antimuscarinic bronchodilator
24023	THEODROX tablets [3M]	aluminium hydroxide/aminophylline		tablets	Oral	Xanthines
24224	CODELSOL injection 16mg/ml [MSD MORSON]	prednisolone sodium phosphate	16mg/ml	injection	Unknown	Prednisolone
24380	sodium cromoglicate with salbutamol inhaler and spacer	salbutamol/sodium cromoglicate		inhaler and spacer	Inhalation	SABA
24418	BIOPHYLLINE tablets 350mg [LOREX]	theophylline	350mg	tablets	Oral	Xanthines
24471	magnesium sulphate injection 10%	magnesium sulphate	10%	injection	Intravenous Infusion	Magnesium sulphate

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
24601	TIXYCOLDS syrup [NOVARTIS]	diphenhydramine hydrochloride/ pseudoephedrine hydrochloride		syrup	Oral	Adrenreceptor Agonist
24645	VENTOLIN concentrate for solution for infusion 5mg/5ml [A & H]	salbutamol sulphate	5mg/5ml	concentrate for solution for infusion	Intravenous Infusion	SABA
24674	BIOPHYLLINE tablets 500mg [LOREX]	theophylline	500mg	tablets	Oral	Xanthines
24898	SPACEHALER BDP SPACEHALER 100micrograms/actuation [CELLTECH]	beclometasone dipropionate	100micrograms /actuation	SPACEHALER	Inhalation	Inhaled Corticosteroid
24934	pseudoephedrine with brompheniramine guaifenesin and phenylpropanolamine expectorant	alcohol/brompheniramine maleate /guaifenesin/pseudoephedrine		expectorant	Oral	Adrenreceptor Agonist
25119	TILADE cfc free inhaler 2mg/inhalation [SANOFI/AVE]	nedocromil sodium	2mg/inhalation	cfc free inhaler	Inhalation	Chromones
25204	BECLOMETASONE aerosol inhaler 100micrograms/actuation [HILLCROSS]	beclometasone dipropionate	100micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
25226	SOLU-MEDRONE injection 125mg [PHARMACIA]	methylprednisolone sodium succinate	125mg	injection	Intravenous Injection	n/a
25272	PRECORTISYL tablets 1mg [HOECHSTMAR]	prednisolone	1mg	tablets	Oral	Prednisolone
25339	MAXIVENT STERIPOULE unit dose nebulising solution 5mg/2.5ml [ASHBOURNE]	salbutamol sulphate	5mg/2.5ml	unit dose nebulising solution	Nebulised	SABA
25593	ephedrine injection 3mg/ml	ephedrine hydrochloride	3mg/ml	injection	Intravenous Injection	Adrenreceptor Agonist
25784	ATIMOS MODULITE cfc free inhaler 12micrograms/actuation [CHIESI]	formoterol fumarate dihydrate	12micrograms/ actuation	cfc free inhaler	Inhalation	Long acting beata agonist
25839	SOLU-MEDRONE injection 1g [PHARMACIA]	methylprednisolone sodium succinate	1g	injection	Intravenous Injection	n/a
26063	BECLOMETASONE aerosol inhaler 100micrograms/actuation [APS]	beclometasone dipropionate	100micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
26616	ipratropium bromide with fenoterol hydrobromide aerosol inhaler 40micrograms + 100micrograms/actuation	fenoterol hydrobromide/ ipratropium bromide	40micrograms + 100mcg/actuation	aerosol inhaler	Unknown	SABA
26744	EXPULIN DECONGESTANT sugar free linctus [SHIRE]	chlorphenamine maleate/ ephedrine hydrochloride		sugar free linctus	Oral	Adrenreceptor Agonist
26860	theophylline with ephedrine sulphate tablets 120mg + 15mg	ephedrine sulphate/theophylline	120mg + 15mg	tablets	Oral	Adrenreceptor Agonist

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
26873	COBUTOLIN tablets 2mg [ACTAVIS]	salbutamol sulphate	2mg	tablets	Oral	SABA
26987	BRICANYL COMPOUND tablets [ASTRAZENEC]	guaifenesin/terbutaline sulphate		tablets	Oral	n/a
27188	EASYHALER BUDESONIDE dry powder inhaler 200micrograms/actuation [ORION]	budesonide	200micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
27249	DO-DO CHESTEZE tablets [NOVARTIS]	caffeine/ephedrine/theophylline		tablets	Oral	Adrenreceptor Agonist
27340	SALBUVENT injection 0.5mg/ml [PHARMACIA]	salbutamol sulphate	0.5mg/ml	injection	Unknown	SABA
27413	DEPO-MEDRONE injection 80mg/2ml [PHARMACIA]	methylprednisolone acetate	80mg/2ml	injection	injection	n/a
27505	ipratropium bromide with fenoterol hydrobromide breath actuated inhaler 40micrograms + 100micrograms/actuation	fenoterol hydrobromide/ipratropium bromide	40micrograms + 100micrograms /actuation	breath actuated inhaler	Unknown	SABA
27679	BECLOMETASONE breath actuated inhaler 100micrograms/actuation [APS]	beclometasone dipropionate	100micrograms /actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
27944	TEDRAL elixir [PARKE]	ephedrine hydrochloride/theophylline		elixir	Oral	Adrenreceptor Agonist
27962	DELTASTAB tablets 1mg [WAYMADE]	prednisolone	1mg	tablets	Oral	Prednisolone
28073	BECLOMETASONE breath actuated inhaler 250micrograms/actuation [APS]	beclometasone dipropionate	250micrograms /actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
28241	MIN-I-JET AMINOPHYLLINE injection 250mg/10ml [UCB]	aminophylline	250mg/10ml	injection	Intravenous Injection	Xanthines
28375	PREDNISOLONE enteric coated tablets 2.5mg [HILLCROSS]	prednisolone	2.5mg	enteric coated tablets	Oral	Prednisolone
28376	PREDNISOLONE enteric coated tablets 2.5mg [BIOREX]	prednisolone	2.5mg	enteric coated tablets	Oral	Prednisolone
28508	SALBUTAMOL aerosol inhaler 100micrograms/inhalation [IVAX]	salbutamol sulphate	100micrograms /inhalation	aerosol inhaler	Inhalation	SABA
28577	VENTOLIN injection 50micrograms/ml [A & H]	salbutamol sulphate	50micrograms/ ml	injection	Subcutaneous Injection	SABA
28640	BECLOMETASONE aerosol inhaler 100micrograms/actuation [ACTAVIS]	beclometasone dipropionate	100micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
28761	SPACEHALER BDP SPACEHALER 50micrograms/actuation [CELLTECH]	beclometasone dipropionate	50micrograms/ actuation	SPACEHALER	Inhalation	Inhaled Corticosteroid
28859	DELTASTAB tablets 5mg [WAYMADE]	prednisolone	5mg	tablets	Oral	Prednisolone
28881	SALBUTAMOL sugar free oral solution [HILLCROSS]	salbutamol sulphate		sugar free oral solution	Oral	SABA

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
29267	SALBUVENT tablets 4mg [PHARMACIA]	salbutamol sulphate	4mg	tablets	Oral	SABA
29273	AMINOPHYLLINE modified release tablet 225mg [HILLCROSS]	aminophylline hydrate	225mg	modified release tablet	Oral	Xanthines
29325	BECLOMETASONE aerosol inhaler 250micrograms/actuation [GEN (UK)]	beclometasone dipropionate	250micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
29333	PREDNISOLONE tablets 5mg [ACTAVIS]	prednisolone	5mg	tablets	Oral	Prednisolone
29730	ephedrine with guaifenesin syrup	ephedrine hydrochloride/guaifenesin		syrup	Oral	Adrenreceptor Agonist
30118	SALBUTAMOL cfc free inhaler 100micrograms/inhalation [APS]	salbutamol sulphate	100micrograms /inhalation	cfc free inhaler	Inhalation	SABA
30204	salbutamol capsules (for inhalation) 200micrograms	salbutamol sulphate	200micrograms	capsules (for inhalation)	Inhalation	SABA
30210	BECLOMETASONE aerosol inhaler 250micrograms/actuation [APS]	beclometasone dipropionate	250micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
30212	salbutamol CYCLOHALER	salbutamol sulphate		CYCLOHALER	Unknown	SABA
30229	IPRATROPIUM BROMIDE unit dose nebuliser solution 250micrograms/ml [GALEN]	ipratropium bromide	250micrograms /ml	unit dose nebuliser solution	Nebulised	Antimuscarinic bronchodilator
30230	salbutamol breath actuated inhaler 100micrograms/actuation	salbutamol sulphate	100micrograms /actuation	breath actuated inhaler	Inhalation	SABA
30238	BECLOMETASONE breath actuated inhaler 50micrograms/actuation [APS]	beclometasone dipropionate	50micrograms/ actuation	breath actuated inhaler	Inhalation	Inhaled Corticosteroid
30240	AEROLIN AUTOHALER cfc free breath actuated inhaler 100micrograms/actuation [3M]	salbutamol sulphate	100micrograms /actuation	cfc free breath actuated inhaler	Inhalation	SABA
30596	AMINOPHYLLINE modified release tablet 225mg [ACTAVIS]	aminophylline hydrate	225mg	modified release tablet	Oral	Xanthines
30649	EASYHALER BUDESONIDE dry powder inhaler 400micrograms/actuation [ORION]	budesonide	400micrograms /actuation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
31082	SALBUVENT respirator solution 5mg/ml [PHARMACIA]	salbutamol sulphate	5mg/ml	respirator solution	Nebulised	SABA
31091	EPHEDRINE HYDROCHLORIDE tablets 15mg [CP PHARM]	ephedrine hydrochloride	15mg	tablets	Oral	Adrenreceptor Agonist
31327	prednisolone steaglate tablets 6.65mg	prednisolone steaglate	6.65mg	tablets	Oral	Prednisolone
31532	PREDNISOLONE enteric coated tablets 5mg [HILLCROSS]	prednisolone	5mg	enteric coated tablets	Oral	Prednisolone
31774	BECLOMETASONE aerosol inhaler 50micrograms/actuation [GEN (UK)]	beclometasone dipropionate	50micrograms/ actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
31845	SALAPIN syrup 2mg/5ml [PINEWOOD]	salbutamol sulphate	2mg/5ml	syrup	Oral	SABA

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
31933	SALBUTAMOL aerosol inhaler 100micrograms/inhalation [HILLCROSS]	salbutamol sulphate	100micrograms /inhalation	aerosol inhaler	Inhalation	SABA
32033	dextromethorphan with ephedrine syrup 7.5mg + 15mg/5ml	dextromethorphan hydrobromide/ephedrine	7.5mg + 15mg/5ml	syrup	Oral	Adrenreceptor Agonist
32050	SALBUTAMOL CYCLOCAPS capsules (for inhalation) 400micrograms [TEVA]	salbutamol sulphate	400micrograms	capsules (for inhalation)	Inhalation	SABA
32102	SALBUTAMOL tablets 4mg [HILLCROSS]	salbutamol sulphate	4mg	tablets	Oral	SABA
32748	ephedrine injection 30mg/1ml	ephedrine hydrochloride	30mg/1ml	injection	Unknown	Adrenreceptor Agonist
32803	PREDNISOLONE enteric coated tablets 5mg [ACTAVIS]	prednisolone	5mg	enteric coated tablets	Oral	Prednisolone
32835	PREDNISOLONE tablets 5mg [WOCKHARDT]	prednisolone	5mg	tablets	Oral	Prednisolone
32874	BECLOMETASONE aerosol inhaler 50micrograms/actuation [ACTAVIS]	beclometasone dipropionate	50micrograms/ actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
33089	SALBUTAMOL aerosol inhaler 100micrograms/inhalation [KENT]	salbutamol sulphate	100micrograms /inhalation	aerosol inhaler	Inhalation	SABA
33132	methylprednisolone acetate injection 40mg/1ml	methylprednisolone acetate	40mg/1ml	injection	injection	n/a
33258	BECLOMETASONE aerosol inhaler 250micrograms/actuation [HILLCROSS]	beclometasone dipropionate	250micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
33373	SALBUTAMOL CYCLOCAPS capsules (for inhalation) 200micrograms [TEVA]	salbutamol sulphate	200micrograms	capsules (for inhalation)	Inhalation	SABA
33434	NORADRAN syrup 7.5mg + 15mg/5ml [NORMA]	dextromethorphan hydrobromide/ephedrine	7.5mg + 15mg/5ml	syrup	Oral	Adrenreceptor Agonist
33588	SALBUTAMOL aerosol inhaler 100micrograms/inhalation [GEN (UK)]	salbutamol sulphate	100micrograms /inhalation	aerosol inhaler	Inhalation	SABA
33642	VICKS COLD & FLU CARE MEDINITE COMPLETE syrup [PROCT&GAMB]	dextromethorphan hydrobromide/ doxylaminesuccinate/paracetamol /pseudoephedrine hydrochloride		syrup	Oral	Adrenreceptor Agonist
33691	PREDNISOLONE enteric coated tablets 5mg [BIOREX]	prednisolone	5mg	enteric coated tablets	Oral	Prednisolone
33817	SALBUTAMOL cfc free inhaler 100micrograms/inhalation [ACTAVIS]	salbutamol sulphate	100micrograms /inhalation	cfc free inhaler	Inhalation	SABA
33849	BECLOMETASONE aerosol inhaler 100micrograms/actuation [NEOLAB]	beclometasone dipropionate	100micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
33988	PREDNISOLONE tablets 5mg [CO-PHARMA]	prednisolone	5mg	tablets	Oral	Prednisolone

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
33990	PREDNISOLONE tablets 5mg [IVAX]	prednisolone	5mg	tablets	Oral	Prednisolone
34018	SALBUTAMOL unit dose nebulising solution 5mg/2.5ml [GALEN]	salbutamol sulphate	5mg/2.5ml	unit dose nebulising solution	Nebulised	SABA
34029	salbutamol capsules (for inhalation) 400micrograms	salbutamol sulphate	400micrograms	capsules (for inhalation)	Inhalation	SABA
34109	prednisolone enteric coated tablets 5mg	prednisolone	5mg	enteric coated tablets	Oral	Prednisolone
34134	AEROLIN 400 aerosol inhaler 100micrograms/actuation [3M]	salbutamol sulphate	100micrograms /actuation	aerosol inhaler	Inhalation	SABA
34162	SALBUTAMOL unit dose nebulising solution 2.5mg/2.5ml [GALEN]	salbutamol sulphate	2.5mg/2.5ml	unit dose nebulising solution	Nebulised	SABA
34310	SALBUTAMOL cfc free inhaler 100micrograms/inhalation [HILLCROSS]	salbutamol sulphate	100micrograms /inhalation	cfc free inhaler	Inhalation	SABA
34311	SALBUTAMOL aerosol inhaler 100micrograms/inhalation [BERK]	salbutamol sulphate	100micrograms /inhalation	aerosol inhaler	Inhalation	SABA
34315	BECLOMETASONE aerosol inhaler 250micrograms/actuation [ACTAVIS]	beclometasone dipropionate	250micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
34393	PREDNISOLONE enteric coated tablets 5mg [TEVA]	prednisolone	5mg	enteric coated tablets	Oral	Prednisolone
34404	PREDNISOLONE tablets 1mg [ACTAVIS]	prednisolone	1mg	tablets	Oral	Prednisolone
34452	PREDNISOLONE tablets 1mg [HILLCROSS]	prednisolone	1mg	tablets	Oral	Prednisolone
34461	PREDNISOLONE enteric coated tablets 2.5mg [ACTAVIS]	prednisolone	2.5mg	enteric coated tablets	Oral	Prednisolone
34618	SALBUTAMOL tablets 2mg [ACTAVIS]	salbutamol sulphate	2mg	tablets	Oral	SABA
34619	SALBUTAMOL cfc free inhaler 100micrograms/inhalation [KENT]	salbutamol sulphate	100micrograms /inhalation	cfc free inhaler	Inhalation	SABA
34631	PREDNISOLONE tablets 1mg [CO-PHARMA]	prednisolone	1mg	tablets	Oral	Prednisolone
34660	PREDNISOLONE tablets 1mg [KENT]	prednisolone	1mg	tablets	Oral	Prednisolone
34702	SALBUTAMOL aerosol inhaler 100micrograms/inhalation [CP PHARM]	salbutamol sulphate	100micrograms /inhalation	aerosol inhaler	Inhalation	SABA
34739	BECLOMETASONE aerosol inhaler 50micrograms/actuation [APS]	beclometasone dipropionate	50micrograms/ actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
34748	PREDNISOLONE tablets 1mg [TEVA]	prednisolone	1mg	tablets	Oral	Prednisolone
34781	PREDNISOLONE tablets 5mg [KENT]	prednisolone	5mg	tablets	Oral	Prednisolone

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
34794	BECLOMETASONE aerosol inhaler 200micrograms/actuation [HILLCROSS]	beclometasone dipropionate	200micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
34859	BECLOMETASONE aerosol inhaler 250micrograms/actuation [NEOLAB]	beclometasone dipropionate	250micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
34914	PREDNISOLONE tablets 1mg [CELLTECH]	prednisolone	1mg	tablets	Oral	Prednisolone
34919	BECLOMETASONE aerosol inhaler 50micrograms/actuation [HILLCROSS]	beclometasone dipropionate	50micrograms/ actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
34938	SALBUTAMOL tablets 4mg [ACTAVIS]	salbutamol sulphate	4mg	tablets	Oral	SABA
34978	PREDNISOLONE tablets 1mg [WOCKHARDT]	prednisolone	1mg	tablets	Oral	Prednisolone
34995	SPIRIVA inhalation powder capsules with device 18 micrograms [BOEH INGL]	tiotropium bromide monohydrate	18 micrograms	inhalation powder capsules with device	Inhalation	Antimuscarinic bronchodilator
35000	SPIRIVA inhalation powder capsules (refill) 18 micrograms [BOEH INGL]	tiotropium bromide monohydrate	18 micrograms	inhalation powder capsules (refill)	Inhalation	Antimuscarinic bronchodilator
35011	tiotropium inhalation powder capsules (refill) 18 micrograms	tiotropium bromide monohydrate	18 micrograms	inhalation powder capsules (refill)	Inhalation	Antimuscarinic bronchodilator
35014	tiotropium inhalation powder capsules with device 18 micrograms	tiotropium bromide monohydrate	18 micrograms	inhalation powder capsules with device	Inhalation	Antimuscarinic bronchodilator
35040	DEPO-MEDRONE injection 120mg/3ml [PHARMACIA]	methylprednisolone acetate	120mg/3ml	injection	injection	n/a
35071	BECODISKS inhalation powder (refill) 200micrograms [A & H]	beclometasone dipropionate	200micrograms	inhalation powder (refill)	Inhalation	Inhaled Corticosteroid
35106	BECODISKS DISKHALER inhalation powder 100micrograms [A & H]	beclometasone dipropionate	100micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid
35107	beclometasone inhalation powder blisters with device 400micrograms	beclometasone dipropionate	400micrograms	inhalation powder blisters with device	Inhalation	Inhaled Corticosteroid
35113	beclometasone inhalation powder blisters (refill) 200micrograms	beclometasone dipropionate	200micrograms	inhalation powder blisters (refill)	Inhalation	Inhaled Corticosteroid
35118	BECODISKS DISKHALER inhalation powder 400micrograms [A & H]	beclometasone dipropionate	400micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid
35154	methylprednisolone acetate with lidocaine injection 80mg/2ml + 20mg/2ml	lidocaine hydrochloride/methylprednisolone acetate	80mg/2ml + 20mg/2ml	injection	Tendon sheath injection	n/a
35156	methylprednisolone acetate with lidocaine injection 40mg/1ml + 10mg/1ml	lidocaine hydrochloride/ methylprednisolone acetate	40mg/1ml + 10mg/1ml	injection	injection	n/a

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
35165	SEREVENT DISKHALER inhalation powder 50micrograms [GLAXO]	salmeterol xinafoate	50micrograms	inhalation powder	Inhalation	Long acting beata agonist
35225	FLIXOTIDE DISKHALER inhalation powder 100micrograms [A & H]	fluticasone propionate	100micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid
35288	beclometasone inhalation powder blisters (refill) 400micrograms	beclometasone dipropionate	400micrograms	inhalation powder blisters (refill)	Inhalation	Inhaled Corticosteroid
35293	beclometasone inhalation powder blisters with device 200micrograms	beclometasone dipropionate	200micrograms	inhalation powder blisters with device	Inhalation	Inhaled Corticosteroid
35299	BECODISKS inhalation powder (refill) 400micrograms [A & H]	beclometasone dipropionate	400micrograms	inhalation powder (refill)	Inhalation	Inhaled Corticosteroid
35374	FLIXOTIDE DISKHALER (REFILL) inhalation powder 500 micrograms [A & H]	fluticasone propionate	500 micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid
35392	FLIXOTIDE DISKHALER inhalation powder 500 micrograms [A & H]	fluticasone propionate	500 micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid
35408	BECODISKS inhalation powder (refill) 100micrograms [A & H]	beclometasone dipropionate	100micrograms	inhalation powder (refill)	Inhalation	Inhaled Corticosteroid
35430	BECODISKS DISKHALER inhalation powder 200micrograms [A & H]	beclometasone dipropionate	200micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid
35461	FLIXOTIDE DISKHALER inhalation powder 250micrograms [A & H]	fluticasone propionate	250micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid
35503	salmeterol inhalation powder blisters (refill) 50micrograms	salmeterol xinafoate	50micrograms	inhalation powder blisters (refill)	Inhalation	Long acting beata agonist
35510	budesonide dry powder inhalation cartridge with device 200micrograms	budesonide	200micrograms	dry powder inhalation cartridge with device	Inhalation	Inhaled Corticosteroid
35522	BRICANYL injection 500micrograms/1ml [ASTRAZENEC]	terbutaline sulphate	500micrograms /1ml	injection	Subcutaneous Injection	SABA
35542	salmeterol inhalation powder blisters with device 50micrograms	salmeterol xinafoate	50micrograms	inhalation powder blisters with device	Inhalation	Long acting beata agonist
35557	IPRAMOL STERI-NEB unit dose nebulising solution 500micrograms + 2.5mg/2.5ml [IVAX]	ipratropium bromide/salbutamol sulphate	500micrograms + 2.5mg/2.5ml	unit dose nebulising solution	Nebulised	Antimuscarinic bronchodilator
35580	beclometasone inhalation powder blisters with device 100micrograms	beclometasone dipropionate	100micrograms	inhalation powder blisters with	Inhalation	Inhaled Corticosteroid

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
				device		
35602	budesonide dry powder inhalation cartridge (refill) 200micrograms	budesonide	200micrograms	dry powder inhalation cartridge (refill)	Inhalation	Inhaled Corticosteroid
35611	FLIXOTIDE DISKHALER (REFILL) inhalation powder 250micrograms [A & H]	fluticasone propionate	250micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid
35631	BUDELIN NOVOLIZER inhalation powder with device 200micrograms [MEDA]	budesonide	200micrograms	inhalation powder with device	Inhalation	Inhaled Corticosteroid
35638	fluticasone inhalation powder blisters with device 100micrograms	fluticasone propionate	100micrograms	inhalation powder blisters with device	Inhalation	Inhaled Corticosteroid
35652	beclometasone inhalation powder blisters (refill) 100micrograms	beclometasone dipropionate	100micrograms	inhalation powder blisters (refill)	Inhalation	Inhaled Corticosteroid
35688	methylprednisolone acetate injection 120mg/3ml	methylprednisolone acetate	120mg/3ml	injection	Tendon sheath injection	n/a
35700	fluticasone inhalation powder blisters with device 500 micrograms	fluticasone propionate	500 micrograms	inhalation powder blisters with device	Inhalation	Inhaled Corticosteroid
35724	BUDELIN NOVOLIZER inhalation powder (refill) 200micrograms [MEDA]	budesonide	200micrograms	inhalation powder (refill)	Inhalation	Inhaled Corticosteroid
35725	EASYHALER FORMOTEROL dry powder inhaler 12micrograms/actuation [ORION]	formoterol fumarate dihydrate	12micrograms/ actuation	dry powder inhaler	Inhalation	Long acting beata agonist
35744	BRICANYL injection 2.5mg/5ml [ASTRAZENEC]	terbutaline sulphate	2.5mg/5ml	injection	Subcutaneous Injection	SABA
35772	fluticasone inhalation powder blisters (refill) 100micrograms	fluticasone propionate	100micrograms	inhalation powder blisters (refill)	Inhalation	Inhaled Corticosteroid
35825	SEREVENT DISKHALER (REFILL) inhalation powder 50micrograms [GLAXO]	salmeterol xinafoate	50micrograms	inhalation powder	Inhalation	Long acting beata agonist
35861	terbutaline injection 2.5mg/5ml	terbutaline sulphate	2.5mg/5ml	injection	Subcutaneous Injection	SABA
35862	terbutaline injection 500micrograms/1ml	terbutaline sulphate	500micrograms /1ml	injection	Subcutaneous Injection	SABA
35905	fluticasone inhalation powder blisters (refill) 250micrograms	fluticasone propionate	250micrograms	inhalation powder blisters (refill)	Inhalation	Inhaled Corticosteroid
35986	FLIXOTIDE DISKHALER (REFILL) inhalation powder 50micrograms [A & H]	fluticasone propionate	50micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
36021	fluticasone inhalation powder blisters with device 50micrograms	fluticasone propionate	50micrograms	inhalation powder blisters with device	Inhalation	Inhaled Corticosteroid
36090	FLIXOTIDE DISKHALER (REFILL) inhalation powder 100micrograms [A & H]	fluticasone propionate	100micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid
36252	ephedrine hydrochloride injection 30mg/10ml	ephedrine hydrochloride	30mg/10ml	injection	Intravenous Injection	Adrenreceptor Agonist
36290	FLIXOTIDE DISKHALER inhalation powder 50micrograms [A & H]	fluticasone propionate	50micrograms	inhalation powder	Inhalation	Inhaled Corticosteroid
36390	ephedrine hydrochloride injection 30mg/1ml	ephedrine hydrochloride	30mg/1ml	injection	Intravenous Injection	Adrenreceptor Agonist
36401	fluticasone inhalation powder blisters with device 250micrograms	fluticasone propionate	250micrograms	inhalation powder blisters with device	Inhalation	Inhaled Corticosteroid
36462	fluticasone inhalation powder blisters (refill) 500 micrograms	fluticasone propionate	500 micrograms	inhalation powder blisters (refill)	Inhalation	Inhaled Corticosteroid
36864	tiotropium inhalation solution 2.5 micrograms/actuation	tiotropium bromide monohydrate	2.5 micrograms / actuation	inhalation solution	Inhalation	Antimuscarinic bronchodilator
36869	SPIRIVA RESPIMAT inhalation solution 2.5 micrograms/actuation [BOEH INGL]	tiotropium bromide monohydrate	2.5 micrograms/ actuation	inhalation solution	Inhalation	Antimuscarinic bronchodilator
37432	FOSTAIR cfc free inhaler 100micrograms + 6micrograms/actuation [CHIESI]	beclometasone dipropionate/ formoterol fumarate dihydrate	100micrograms + 6micrograms/ actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
37447	fluticasone inhalation powder blisters (refill) 50micrograms	fluticasone propionate	50micrograms	inhalation powder blisters (refill)	Inhalation	Inhaled Corticosteroid
37470	beclometasone extrafine particle with formoterol cfc free inhaler 100micrograms + 6micrograms/actuation	beclometasone dipropionate/ formoterol fumarate dihydrate	100micrograms +6micrograms/ actuation	cfc free inhaler	Inhalation	Inhaled Corticosteroid
37612	TERBUTALINE unit dose nebulising solution 2.5mg/ml [GALEN]	terbutaline sulphate	2.5mg/ml	unit dose nebulising solution	Nebulised	SABA
37615	sodium cromoglicate aerosol inhaler 1mg/inhalation	sodium cromoglicate	1mg/inhalation	aerosol inhaler	Inhalation	Chromones
37791	ipratropium bromide inhalation solution 250micrograms/ml	ipratropium bromide	250micrograms /ml	inhalation solution	Nebulised	Antimuscarinic bronchodilator
38079	salbutamol dry powder inhalation cartridge with device 100micrograms	salbutamol sulphate	100micrograms	dry powder inhalation	Inhalation	SABA

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
				cartridge with device		
38097	SALBUTAMOL CYCLOCAPS 200micrograms [DU PONT]	salbutamol sulphate	200micrograms	CYCLOCAPS	Inhalation	SABA
38120	theophylline modified release tablet 500mg	theophylline	500mg	modified release tablet	Oral	Xanthines
38136	SALBULIN MDPI NOVOLIZER dry powder inhalation cartridge with device 100micrograms [MEDA]	salbutamol sulphate	100micrograms	dry powder inhalation cartridge with device	Inhalation	SABA
38214	salbutamol dry powder inhalation cartridge (refill) 100micrograms	salbutamol sulphate	100micrograms	dry powder inhalation cartridge (refill)	Inhalation	SABA
38226	SALBULIN MDPI NOVOLIZER dry powder inhalation cartridge (refill) 100micrograms [MEDA]	salbutamol sulphate	100micrograms	dry powder inhalation cartridge (refill)	Inhalation	SABA
38347	magnesium sulphate injection 20%	magnesium sulphate	20%	injection	Intravenous Injection	Magnesium sulphate
38407	prednisolone (ipu) tablets 20mg	prednisolone	20mg	tablets	Oral	Prednisolone
38416	SALBUTAMOL CYCLOCAPS 400micrograms [DU PONT]	salbutamol sulphate	400micrograms	CYCLOCAPS	Inhalation	SABA
38419	TERBUTALINE syrup 1.5mg/5ml [HILLCROSS]	terbutaline sulphate	1.5mg/5ml	syrup	Oral	SABA
38471	sodium cromoglicate cfc free inhaler 5mg	sodium cromoglicate	5mg	cfc free inhaler	Inhalation	Chromones
38501	INTAL cfc free inhaler 5mg [SANOFI/AVE]	sodium cromoglicate	5mg	cfc free inhaler	Inhalation	Chromones
39040	PHYLLOCONTIN FORTE CONTINUS tablets 350mg [NAPPPHARM]	aminophylline hydrate	350mg	tablets	Oral	Xanthines
39067	CLIPPER gastro-resistant modified release tablets 5mg [CHIESI]	beclometasone dipropionate	5mg	gastro-resistant modified release tablets	Oral	Inhaled Corticosteroid
39099	PULMICORT cfc free inhaler 100micrograms [ASTRAZENEC]	budesonide	100micrograms	cfc free inhaler	Inhalation	Inhaled Corticosteroid
39102	budesonide cfc free inhaler 100micrograms	budesonide	100micrograms	cfc free inhaler	Inhalation	Inhaled Corticosteroid
39200	AEROBEC FORTE AUTOHALER 250micrograms/actuation [MEDA]	beclometasone dipropionate	250micrograms /actuation	AUTOHALER	Inhalation	Inhaled Corticosteroid
39239	ephedrine hydrochloride injection 30mg/10ml	ephedrine hydrochloride	30mg/10ml	injection	Intravenous Injection	Adrenreceptor Agonist
39879	budesonide cfc free inhaler 200micrograms	budesonide	200micrograms	cfc free inhaler	Inhalation	Inhaled Corticosteroid
40057	PULMICORT cfc free inhaler 200micrograms [ASTRAZENEC]	budesonide	200micrograms	cfc free inhaler	Inhalation	Inhaled Corticosteroid
40177	IPRATROPIUM BROMIDE unit dose nebulising solution	ipratropium bromide	250micrograms	unit dose	Nebulised	Antimuscarinic

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
	250micrograms/ml [HILLCROSS]		/ml	nebulising solution		bronchodilator
40599	STERIPOULE SALBUTAMOL unit dose nebuliser solution 5mg/2.5ml [GALEN]	salbutamol sulphate	5mg/2.5ml	unit dose nebuliser solution	Nebulised	SABA
40637	STERIPOULE IPRATROPIUM unit dose nebuliser solution 250micrograms/ml [GALEN]	ipratropium bromide	250micrograms /ml	unit dose nebuliser solution	Nebulised	Antimuscarinic bronchodilator
40655	SALBUVENT aerosol inhaler 100micrograms/actuation [PHARMACIA]	salbutamol sulphate	100micrograms /actuation	aerosol inhaler	Inhalation	SABA
40709	SALBUTAMOL unit dose nebulising solution 2.5mg/2.5ml [HILLCROSS]	salbutamol sulphate	2.5mg/2.5ml	unit dose nebulising solution	Nebulised	SABA
40832	STERIPOULE IPRATROPIUM unit dose nebuliser solution 500micrograms/2ml [GALEN]	ipratropium bromide	500micrograms /2ml	unit dose nebuliser solution	Nebulised	Antimuscarinic bronchodilator
41187	MAGNESIUM SULPHATE injection 50% [CELLTECH]	magnesium sulphate	50%	injection	Intravenous Infusion	Magnesium sulphate
41269	BECLOMETASONE CYCLOCAPS capsules (for inhalation) 400micrograms [TEVA]	beclometasone dipropionate	400micrograms	capsules (for inhalation)	Inhalation	Inhaled Corticosteroid
41287	XOLAIR injection 150mg [NOVARTIS]	omalizumab	150mg	injection	Subcutaneous Injection	Anti IgE agents
41412	beclometasone aerosol inhaler 400micrograms/actuation	beclometasone dipropionate	400micrograms /actuation	aerosol inhaler	Inhalation	Inhaled Corticosteroid
41515	PREDNISOLONE tablets 5mg [TEVA]	prednisolone	5mg	tablets	Oral	Prednisolone
41548	SALBUTAMOL tablets 2mg [APS]	salbutamol sulphate	2mg	tablets	Oral	SABA
41549	SALBUTAMOL tablets 2mg [CP PHARM]	salbutamol sulphate	2mg	tablets	Oral	SABA
41691	SALBUTAMOL sugar free oral solution 2mg/5ml [SANDOZ]	salbutamol sulphate	2mg/5ml	sugar free oral solution	Oral	SABA
41745	PREDNISOLONE tablets 25mg [WINTHROP]	prednisolone	25mg	tablets	Oral	Prednisolone
41832	MONOVENT syrup 1.5mg/5ml [SANDOZ]	terbutaline sulphate	1.5mg/5ml	syrup	Oral	SABA
42279	STERIPOULE SALBUTAMOL unit dose nebuliser solution 2.5mg/2.5ml [GALEN]	salbutamol sulphate	2.5mg/2.5ml	unit dose nebuliser solution	Nebulised	SABA
42497	salbutamol tablets 8mg	salbutamol	8mg	tablets	Oral	SABA
42511	AMINOPHYLLINE injection 25mg/ml [CELLTECH]	aminophylline	25mg/ml	injection	Intravenous Injection	Xanthines
42830	VENTOLIN EVOHALER cfc free inhaler 100micrograms/inhalation [GLAXO]	salbutamol sulphate	100micrograms /inhalation	cfc free inhaler	Inhalation	SABA
42858	VENTOLIN ACCUHALER dry powder inhaler	salbutamol sulphate	200micrograms	dry powder	Inhalation	SABA

Pegasus code	Product name	drug substance name	subs strength	formulation	route	category
	200micrograms/actuation [GLAXO]		/actuation	inhaler		
42867	TERBUTALINE syrup 1.5mg/5ml [SANDOZ]	terbutaline sulphate	1.5mg/5ml	syrup	Oral	SABA
42886	BRICANYL TURBOHALER dry powder inhaler 500micrograms [ASTRAZENEC]	terbutaline sulphate	500micrograms	dry powder inhaler	Inhalation	SABA
42910	AMINOPHYLLINE injection 250mg/10ml [MARTINDALE]	aminophylline	250mg/10ml	injection	Intravenous Injection	Xanthines
42928	FLIXOTIDE ACCUHALER dry powder inhaler 100micrograms/inhalation [A & H]	fluticasone propionate	100micrograms /inhalation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
42985	FLIXOTIDE ACCUHALER dry powder inhaler 50micrograms/inhalation [A & H]	fluticasone propionate	50micrograms/inhalation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
42994	FLIXOTIDE ACCUHALER dry powder inhaler 250micrograms/inhalation [A & H]	fluticasone propionate	250micrograms /inhalation	dry powder inhaler	Inhalation	Inhaled Corticosteroid
43046	SALIPRANEB unit dose nebulising solution 500micrograms + 2.5mg/2.5ml [BREATH]	ipratropium bromide/salbutamol sulphate	500micrograms + 2.5mg/2.5ml	unit dose nebulising solution	Nebulised	Antimuscarinic bronchodilator

Appendix 8. Inhaled corticosteroid codes- 237 prodcodes

pegasus code	Product name	drug substance name	Substance strength	formulation	route
6746	budesonide with formoterol dry powder inhaler 400micrograms + 12micrograms/actuation	budesonide/formoterol fumarate dihydrate	400micrograms + 12micrograms/actuation	dry powder inhaler	Inhalation
18537	budesonide capsules (for inhalation) 200micrograms	budesonide	200micrograms	capsules (for inhalation)	Inhalation
2229	BECODISKS disc 100micrograms [A & H]	beclometasone dipropionate	100micrograms	disc	Inhalation
1951	BECODISKS disc 400micrograms [A & H]	beclometasone dipropionate	400micrograms	disc	Inhalation
883	BECODISKS disc 200micrograms [A & H]	beclometasone dipropionate	200micrograms	disc	Inhalation
35772	fluticasone inhalation powder blisters (refill) 100micrograms	fluticasone propionate	100micrograms	inhalation powder blisters (refill)	Inhalation
17654	EASYHALER BECLOMETASONE dry powder inhaler 200micrograms/actuation [ORION]	beclometasone dipropionate	200micrograms/actuation	dry powder inhaler	Inhalation
665	SERETIDE 100 ACCUHALER dry powder inhaler [GLAXO]	salmeterol xinafoate/fluticasone propionate		dry powder inhaler	Inhalation
3289	FLIXOTIDE aerosol inhaler 25micrograms/actuation [A & H]	fluticasone propionate	25micrograms/actuation	aerosol inhaler	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
1676	FLIXOTIDE aerosol inhaler 125micrograms/actuation [A & H]	fluticasone propionate	125micrograms/actuation	aerosol inhaler	Inhalation
1518	FLIXOTIDE aerosol inhaler 50micrograms/actuation [A & H]	fluticasone propionate	50micrograms/actuation	aerosol inhaler	Inhalation
3075	BECOTIDE ROTACAPS 400micrograms [A & H]	beclometasone dipropionate	400micrograms	ROTACAPS	Inhalation
3947	BECOTIDE ROTACAPS 100micrograms [A & H]	beclometasone dipropionate	100micrograms	ROTACAPS	Inhalation
35106	BECODISKS DISKHALER inhalation powder 100micrograms [A & H]	beclometasone dipropionate	100micrograms	inhalation powder	Inhalation
6839	ALVESCO cfc free inhaler 160micrograms/actuation [NYCOMED]	ciclesonide	160micrograms/actuation	cfc free inhaler	Inhalation
35392	FLIXOTIDE DISKHALER inhalation powder 500 micrograms [A & H]	fluticasone propionate	500 micrograms	inhalation powder	Inhalation
35299	BECODISKS inhalation powder (refill) 400micrograms [A & H]	beclometasone dipropionate	400micrograms	inhalation powder (refill)	Inhalation
40057	PULMICORT cfc free inhaler 200micrograms [ASTRAZENEC]	budesonide	200micrograms	cfc free inhaler	Inhalation
30238	BECLOMETASONE breath actuated inhaler 50micrograms/actuation [APS]	beclometasone dipropionate	50micrograms/actuation	breath actuated inhaler	Inhalation
1551	BECLAZONE aerosol inhaler 250micrograms/actuation [IVAX]	beclometasone dipropionate	250micrograms/actuation	aerosol inhaler	Inhalation
2951	fluticasone aerosol inhaler 250micrograms/actuation	fluticasone propionate	250micrograms/actuation	aerosol inhaler	Inhalation
5885	fluticasone dry powder inhaler 100micrograms/inhalation	fluticasone propionate	100micrograms/inhalation	dry powder inhaler	Inhalation
9164	fluticasone dry powder inhaler 50micrograms/inhalation	fluticasone propionate	50micrograms/inhalation	dry powder inhaler	Inhalation
6938	salmeterol with fluticasone dry powder inhaler 50micrograms + 100micrograms/inhalation	salmeterol xinafoate/fluticasone propionate	50micrograms + 100micrograms/inhalation	dry powder inhaler	Inhalation
5942	salmeterol with fluticasone dry powder inhaler 50micrograms + 250micrograms/inhalation	salmeterol xinafoate/fluticasone propionate	50micrograms + 250 micrograms/ inhalation	dry powder inhaler	Inhalation
35071	BECODISKS inhalation powder (refill) 200micrograms [A & H]	beclometasone dipropionate	200micrograms	inhalation powder (refill)	Inhalation
454	PULMICORT aerosol inhaler 200micrograms [ASTRAZENEC]	budesonide	200micrograms	aerosol inhaler	Inhalation
2125	PULMICORT refill canister 200micrograms [ASTRAZENEC]	budesonide	200micrograms	refill canister	Inhalation
1426	FLIXOTIDE disc 500micrograms [A & H]	fluticasone propionate	500micrograms	disc	Inhalation
34859	BECLOMETASONE aerosol inhaler 250micrograms/actuation [NEOLAB]	beclometasone dipropionate	250micrograms/actuation	aerosol inhaler	Inhalation
7602	fluticasone disc 50micrograms	fluticasone propionate	50micrograms	disc	Inhalation
4131	fluticasone disc 100micrograms	fluticasone propionate	100micrograms	disc	Inhalation
7638	fluticasone disc 250micrograms	fluticasone propionate	250micrograms	disc	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
35724	BUDELIN NOVOLIZER inhalation powder (refill) 200micrograms [MEDA]	budesonide	200micrograms	inhalation powder (refill)	Inhalation
42985	FLIXOTIDE ACCUHALER dry powder inhaler 50micrograms/inhalation [A & H]	fluticasone propionate	50micrograms/inhalation	dry powder inhaler	Inhalation
1242	beclometasone aerosol inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms/actuation	aerosol inhaler	Inhalation
38	beclometasone aerosol inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms/actuation	aerosol inhaler	Inhalation
3018	beclometasone aerosol inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/act	aerosol inhaler	Inhalation
16158	CLENIL MODULITE cfc free inhaler 50micrograms/actuation [CHIESI]	beclometasone dipropionate	50micrograms/actuation	cfc free inhaler	Inhalation
638	SERETIDE 250 ACCUHALER dry powder inhaler [GLAXO]	salmeterol xinafoate/fluticasone propionate		dry powder inhaler	Inhalation
5161	SERETIDE 125 EVOHALER cfc free inhaler 25micrograms + 125micrograms/actuation [A & H]	salmeterol xinafoate/fluticasone propionate	25micrograms + 125micrograms/actuation	cfc free inhaler	Inhalation
11497	beclometasone dry powder inhaler 400micrograms/actuation	beclometasone dipropionate	400micrograms/actuation	dry powder inhaler	Inhalation
5521	beclometasone dry powder inhaler 200micrograms/actuation	beclometasone dipropionate	200micrograms/actuation	dry powder inhaler	Inhalation
5804	beclometasone dry powder inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms/actuation	dry powder inhaler	Inhalation
9921	beclometasone extra fine particle cfc free breath actuated inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms/actuation	cfc free breath actuated inhaler	Inhalation
11732	beclometasone extra fine particle cfc free breath actuated inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/actuation	cfc free breath actuated inhaler	Inhalation
25204	BECLOMETASONE aerosol inhaler 100micrograms/actuation [HILLCROSS]	beclometasone dipropionate	100micrograms/actuation	aerosol inhaler	Inhalation
41412	beclometasone aerosol inhaler 400micrograms/actuation	beclometasone dipropionate	400micrograms/actuation	aerosol inhaler	Inhalation
16148	CLENIL MODULITE cfc free inhaler 250micrograms/actuation [CHIESI]	beclometasone dipropionate	250micrograms/actuation	cfc free inhaler	Inhalation
36462	fluticasone inhalation powder blisters (refill) 500 micrograms	fluticasone propionate	500 micrograms	inhalation powder blisters (refill)	Inhalation
1100	BECLAZONE aerosol inhaler 100micrograms/actuation [IVAX]	beclometasone dipropionate	100micrograms/actuation	aerosol inhaler	Inhalation
2992	BECLAZONE aerosol inhaler 50micrograms/actuation [IVAX]	beclometasone dipropionate	50micrograms/actuation	aerosol inhaler	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
37432	FOSTAIR cfc free inhaler 100micrograms + 6micrograms/actuation [CHIESI]	beclometasone dipropionate/formoterol fumarate dihydrate	100micrograms + 6micrograms/actuation	cfc free inhaler	Inhalation
7948	fluticasone dry powder inhaler 250micrograms/inhalation	fluticasone propionate	250micrograms/inhalation	dry powder inhaler	Inhalation
2282	fluticasone dry powder inhaler 500micrograms/inhalation	fluticasone propionate	500micrograms/inhalation	dry powder inhaler	Inhalation
1406	BECOTIDE 50 aerosol inhaler 50micrograms/actuation [A & H]	beclometasone dipropionate	50micrograms/actuation	aerosol inhaler	Inhalation
2335	QVAR cfc free inhaler 100micrograms/actuation [IVAX]	beclometasone dipropionate	100micrograms/actuation	cfc free inhaler	Inhalation
3546	QVAR cfc free inhaler 50micrograms/actuation [IVAX]	beclometasone dipropionate	50micrograms/actuation	cfc free inhaler	Inhalation
1734	beclometasone breath actuated inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms/actuation	breath actuated inhaler	Inhalation
16584	beclometasone cfc free inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/actuation	cfc free inhaler	Inhalation
10102	ciclesonide cfc free inhaler 160micrograms/actuation	ciclesonide	160micrograms/actuation	cfc free inhaler	Inhalation
11307	salbutamol with beclometasone aerosol inhaler 100mcg + 50mcg	beclometasone dipropionate/salbutamol	100mcg + 50mcg	aerosol inhaler	Inhalation
14561	salbutamol with beclometasone capsules (for inhalation) 400micrograms + 200micrograms	beclometasone dipropionate/salbutamol	400micrograms + 200micrograms	capsules (for inhalation)	Inhalation
18456	salbutamol with beclometasone capsules (for inhalation) 200micrograms + 100micrograms	beclometasone dipropionate/salbutamol	200micrograms + 100micrograms	capsules (for inhalation)	Inhalation
37470	beclometasone extra fine particle with formoterol cfc free inhaler 100micrograms + 6micrograms/actuation	beclometasone dipropionate/formoterol fumarate dihydrate	100micrograms + 6micrograms/actuation	cfc free inhaler	Inhalation
14757	PULVINAL BECLOMETASONE DIPROPIONATE dry powder inhaler 100micrograms/actuation [CHIESI]	beclometasone dipropionate	100micrograms/actuation	dry powder inhaler	Inhalation
14736	PULVINAL BECLOMETASONE DIPROPIONATE dry powder inhaler 400micrograms/actuation [CHIESI]	beclometasone dipropionate	400micrograms/actuation	dry powder inhaler	Inhalation
13037	PULVINAL BECLOMETASONE DIPROPIONATE dry powder inhaler 200micrograms/actuation [CHIESI]	beclometasone dipropionate	200micrograms/actuation	dry powder inhaler	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
35580	beclometasone inhalation powder blisters with device 100micrograms	beclometasone dipropionate	100micrograms	inhalation powder blisters with device	Inhalation
30649	EASYHALER BUDESONIDE dry powder inhaler 400micrograms/actuation [ORION]	budesonide	400micrograms/actuation	dry powder inhaler	Inhalation
35408	BECODISKS inhalation powder (refill) 100micrograms [A & H]	beclometasone dipropionate	100micrograms	inhalation powder (refill)	Inhalation
5718	FLIXOTIDE EVOHALER cfc free inhaler 125micrograms/actuation [A&H]	fluticasone propionate	125micrograms/actuation	cfc free inhaler	Inhalation
5309	FLIXOTIDE EVOHALER cfc free inhaler 50micrograms/actuation [A & H]	fluticasone propionate	50micrograms/actuation	cfc free inhaler	Inhalation
5683	FLIXOTIDE EVOHALER cfc free inhaler 250micrograms/actuation [A & H]	fluticasone propionate	250micrograms/actuation	cfc free inhaler	Inhalation
1537	BECOTIDE ROTACAPS 200micrograms [A & H]	beclometasone dipropionate	200micrograms	ROTACAPS	Inhalation
28640	BECLOMETASONE aerosol inhaler 100micrograms/actuation [ACTAVIS]	beclometasone dipropionate	100micrograms/actuation	aerosol inhaler	Inhalation
6780	SYMBICORT TURBOHALER dry powder inhaler 400micrograms + 12micrograms/actuation [ASTRAZENEC]	budesonide/formoterol fumarate dihydrate	400micrograms + 12 micrograms/actuation	dry powder inhaler	Inhalation
35461	FLIXOTIDE DISKHALER inhalation powder 250micrograms [A & H]	fluticasone propionate	250micrograms	inhalation powder	Inhalation
1424	FLIXOTIDE disc 250micrograms [A & H]	fluticasone propionate	250micrograms	disc	Inhalation
3989	FLIXOTIDE disc 100micrograms [A & H]	fluticasone propionate	100micrograms	disc	Inhalation
8635	FLIXOTIDE disc 50micrograms [A & H]	fluticasone propionate	50micrograms	disc	Inhalation
37447	fluticasone inhalation powder blisters (refill) 50micrograms	fluticasone propionate	50micrograms	inhalation powder blisters (refill)	Inhalation
4545	PULMICORT LS refill canister 50micrograms [ASTRAZENEC]	budesonide	50micrograms	refill canister	Inhalation
13290	CLENIL MODULITE cfc free inhaler 100micrograms/actuation [CHIESI]	beclometasone dipropionate	100micrograms/actuation	cfc free inhaler	Inhalation
8111	BECLOFORTE VM pack 250micrograms/actuation [A & H]	beclometasone dipropionate	250micrograms/actuation	VM pack	Inhalation
1236	BECLOFORTE aerosol inhaler 250micrograms/actuation [A & H]	beclometasone dipropionate	250micrograms/actuation	aerosol inhaler	Inhalation
23741	NOVOLIZER BUDESONIDE breath actuated dry powder inhaler 200micrograms/actuation [MEDA]	budesonide	200micrograms/actuation	breath actuated dry powder inhaler	Inhalation
35225	FLIXOTIDE DISKHALER inhalation powder 100micrograms [A & H]	fluticasone propionate	100micrograms	inhalation powder	Inhalation
9477	ASMABEC SPACEHALER 100micrograms/actuation [CELLTECH]	beclometasone dipropionate	100micrograms/actuation	SPACEHALER	Inhalation
14590	ASMABEC SPACEHALER 250micrograms/actuation [CELLTECH]	beclometasone dipropionate	250micrograms/actuation	SPACEHALER	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
19389	ASMABEC SPACEHALER 50micrograms/actuation [CELLTECH]	beclometasone dipropionate	50micrograms/actuation	SPACEHALER	Inhalation
35631	BUDELIN NOVOLIZER inhalation powder with device 200micrograms [MEDA]	budesonide	200micrograms	inhalation powder with device	Inhalation
42928	FLIXOTIDE ACCUHALER dry powder inhaler 100micrograms/inhalation [A & H]	fluticasone propionate	100micrograms/inhalation	dry powder inhaler	Inhalation
18848	QVAR EASI-BREATHE cfc free breath actuated inhaler 100micrograms/actuation [IVAX]	beclometasone dipropionate	100micrograms/actuation	cfc free breath actuated inhaler	Inhalation
36401	fluticasone inhalation powder blisters with device 250micrograms	fluticasone propionate	250micrograms	inhalation powder blisters with device	Inhalation
1552	BECLOFORTE EASI-BREATHE breath actuated inhaler 250micrograms/actuation [A & H]	beclometasone dipropionate	250micrograms/actuation	breath actuated inhaler	Inhalation
2600	beclometasone breath actuated inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms/actuation	breath actuated inhaler	Inhalation
2160	beclometasone breath actuated inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/actuation	breath actuated inhaler	Inhalation
39879	budesonide cfc free inhaler 200micrograms	budesonide	200micrograms	cfc free inhaler	Inhalation
41269	BECLOMETASONE CYCLOCAPS capsules (for inhalation) 400micrograms [TEVA]	beclometasone dipropionate	400micrograms	capsules (for inhalation)	Inhalation
3220	QVAR AUTOHALER cfc free breath actuated inhaler 50micrograms/actuation [IVAX]	beclometasone dipropionate	50micrograms/actuation	cfc free breath actuated inhaler	Inhalation
4413	QVAR AUTOHALER cfc free breath actuated inhaler 100micrograms/actuation [IVAX]	beclometasone dipropionate	100micrograms/actuation	cfc free breath actuated inhaler	Inhalation
908	PULMICORT TURBOHALER dry powder inhaler 400micrograms/actuation [ASTRAZENEC]	budesonide	400micrograms/actuation	dry powder inhaler	Inhalation
956	PULMICORT TURBOHALER dry powder inhaler 200micrograms/actuation [ASTRAZENEC]	budesonide	200micrograms/actuation	dry powder inhaler	Inhalation
19031	BDP SPACEHALER 100micrograms/actuation [CELLTECH]	beclometasone dipropionate	100micrograms/actuation	SPACEHALER	Inhalation
17670	EASYHALER BUDESONIDE dry powder inhaler 100micrograms/actuation [ORION]	budesonide	100micrograms/actuation	dry powder inhaler	Inhalation
1725	BECLAZONE EASI-BREATHE breath actuated inhaler 50micrograms/actuation [IVAX]	beclometasone dipropionate	50micrograms/actuation	breath actuated inhaler	Inhalation
1243	BECLAZONE EASI-BREATHE breath actuated inhaler 250micrograms/actuation [IVAX]	beclometasone dipropionate	250micrograms/actuation	breath actuated inhaler	Inhalation
960	PULMICORT TURBOHALER dry powder inhaler 100micrograms/actuation [ASTRAZENEC]	budesonide	100micrograms/actuation	dry powder inhaler	Inhalation
29325	BECLOMETASONE aerosol inhaler 250micrograms/actuation [GEN (UK)]	beclometasone dipropionate	250micrograms/actuation	aerosol inhaler	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
35293	beclometasone inhalation powder blisters with device 200micrograms	beclometasone dipropionate	200micrograms	inhalation powder blisters with device	Inhalation
1885	BECLAZONE aerosol inhaler 200micrograms/actuation [IVAX]	beclometasone dipropionate	200micrograms/actuation	aerosol inhaler	Inhalation
16018	mometasone furoate dry powder inhaler 200micrograms/actuation	mometasone furoate	200micrograms/actuation	dry powder inhaler	Inhalation
1412	FLIXOTIDE aerosol inhaler 250micrograms/actuation [A & H]	fluticasone propionate	250micrograms/actuation	aerosol inhaler	Inhalation
5580	FLIXOTIDE ACCUHALER 50micrograms/inhalation [A & H]	fluticasone propionate	50micrograms/inhalation	ACCUHALER	Inhalation
4926	FLIXOTIDE ACCUHALER 100micrograms/inhalation [A & H]	fluticasone propionate	100micrograms/inhalation	ACCUHALER	Inhalation
2148	beclometasone disc 400micrograms	beclometasone dipropionate	400micrograms	disc	Inhalation
2893	beclometasone disc 200micrograms	beclometasone dipropionate	200micrograms	disc	Inhalation
4365	beclometasone disc 100micrograms	beclometasone dipropionate	100micrograms	disc	Inhalation
5172	SERETIDE 250 EVOHALER cfc free inhaler 25micrograms + 250micrograms/actuation [A & H]	salmeterol xinafoate/ fluticasone propionate	25micrograms + 250 micrograms/actuation	cfc free inhaler	Inhalation
7356	ciclesonide cfc free inhaler 80micrograms/actuation	ciclesonide	80micrograms/actuation	cfc free inhaler	Inhalation
27188	EASYHALER BUDESONIDE dry powder inhaler 200micrograms/actuation [ORION]	budesonide	200micrograms/actuation	dry powder inhaler	Inhalation
15326	beclometasone cfc free inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms/actuation	cfc free inhaler	Inhalation
34428	BECLOMETASONE aerosol inhaler 50micrograms/actuation [NEOLAB]	beclometasone dipropionate	50micrograms/actuation	aerosol inhaler	Inhalation
17590	ASMANEX TWISTHALER dry powder inhaler 400micrograms/actuation [SCHERING-P]	mometasone furoate	400micrograms/actuation	dry powder inhaler	Inhalation
2723	fluticasone aerosol inhaler 25micrograms/actuation	fluticasone propionate	25micrograms/actuation	aerosol inhaler	Inhalation
13815	BECLAZONE aerosol inhaler 100micrograms/actuation [ACTAVIS]	beclometasone dipropionate	100micrograms/actuation	aerosol inhaler	Inhalation
4803	BECLAZONE aerosol inhaler 250micrograms/actuation [ACTAVIS]	beclometasone dipropionate	250micrograms/actuation	aerosol inhaler	Inhalation
9599	BECLAZONE aerosol inhaler 50micrograms/actuation [ACTAVIS]	beclometasone dipropionate	50micrograms/actuation	aerosol inhaler	Inhalation
5992	beclometasone dry powder inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/actuation	dry powder inhaler	Inhalation
19401	beclometasone inhaler with compact spacer 250micrograms/actuation	beclometasone dipropionate	250micrograms/actuation	inhaler with compact spacer	Inhalation
28761	SPACEHALER BDP SPACEHALER 50micrograms/actuation [CELLTECH]	beclometasone dipropionate	50micrograms/ actuation	SPACEHALER	Inhalation
20825	SPACEHALER BDP SPACEHALER 250micrograms/actuation [CELLTECH]	beclometasone dipropionate	250micrograms/actuation	SPACEHALER	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
24898	SPACEHALER BDP SPACEHALER 100micrograms/actuation [CELLTECH]	beclometasone dipropionate	100micrograms/actuation	SPACEHALER	Inhalation
5558	salmeterol with fluticasone dry powder inhaler 50micrograms+ 500micrograms/inhalation	salmeterol xinafoate/fluticasone propionate	50micrograms+ 500micrograms/inhalation	dry powder inhaler	Inhalation
35118	BECODISKS DISKHALER inhalation powder 400micrograms [A & H]	beclometasone dipropionate	400micrograms	inhalation powder	Inhalation
3666	SERETIDE 500 ACCUHALER dry powder inhaler [GLAXO]	salmeterol xinafoate/ fluticasone propionate		dry powder inhaler	Inhalation
16151	CLENIL MODULITE cfc free inhaler 200micrograms/actuation [CHIESI]	beclometasone dipropionate	200micrograms/actuation	cfc free inhaler	Inhalation
10218	budesonide with formoterol dry powder inhaler 100micrograms + 6micrograms/actuation	budesonide/formoterol fumarate dihydrate	100micrograms + 6micrograms/actuation	dry powder inhaler	Inhalation
6796	budesonide with formoterol dry powder inhaler 200micrograms + 6micrograms/actuation	budesonide/formoterol fumarate dihydrate	200micrograms + 6micrograms/actuation	dry powder inhaler	Inhalation
4688	fluticasone aerosol inhaler 50micrograms/actuation	fluticasone propionate	50micrograms/actuation	aerosol inhaler	Inhalation
4132	fluticasone aerosol inhaler 125micrograms/actuation	fluticasone propionate	125micrograms/actuation	aerosol inhaler	Inhalation
3119	BECLOFORTE INTEGRA inhaler with compact spacer 250micrograms/actuation [GLAXO]	beclometasone dipropionate	250micrograms/actuation	inhaler with compact spacer	Inhalation
39102	budesonide cfc free inhaler 100micrograms	Budesonide	100micrograms	cfc free inhaler	Inhalation
18484	VENTIDE paediatric ROTACAPS [A & H]	beclometasone dipropionate/salbutamol		paediatric ROTACAPS	Inhalation
16625	VENTIDE ROTACAPS [A & H]	beclometasone dipropionate/salbutamol		ROTACAPS	Inhalation
5522	beclometasone dry powder inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms/actuation	dry powder inhaler	Inhalation
2440	FLIXOTIDE ACCUHALER 500micrograms/inhalation [A & H]	fluticasone propionate	500micrograms/inhalation	ACCUHALER	Inhalation
911	FLIXOTIDE ACCUHALER 250micrograms/inhalation [A & H]	fluticasone propionate	250micrograms/inhalation	ACCUHALER	Inhalation
35510	budesonide dry powder inhalation cartridge with device 200micrograms	budesonide	200micrograms	dry powder inhalation cartridge with device	Inhalation
30210	BECLOMETASONE aerosol inhaler 250micrograms/actuation [APS]	beclometasone dipropionate	250micrograms/actuation	aerosol inhaler	Inhalation
1801	VENTIDE aerosol inhaler [A & H]	beclometasone dipropionate/salbutamol		aerosol inhaler	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
3927	FILAIR aerosol inhaler 100micrograms/actuation [MEDA]	beclometasone dipropionate	100micrograms/actuation	aerosol inhaler	Inhalation
3743	FILAIR aerosol inhaler 50micrograms/actuation [MEDA]	beclometasone dipropionate	50micrograms/actuation	aerosol inhaler	Inhalation
35638	fluticasone inhalation powder blisters with device 100micrograms	fluticasone propionate	100micrograms	inhalation powder blisters with device	Inhalation
5864	salmeterol with fluticasone cfc free inhaler 25micrograms + 250micrograms/actuation	salmeterol xinafoate /fluticasone propionate	25micrograms + 250 micrograms/actuation	cfc free inhaler	Inhalation
6569	salmeterol with fluticasone cfc free inhaler 25micrograms + 125micrograms/actuation	salmeterol xinafoate/fluticasone propionate	25micrograms + 125 micrograms/actuation	cfc free inhaler	Inhalation
6616	salmeterol with fluticasone cfc free inhaler 25micrograms + 50micrograms/actuation	salmeterol xinafoate/ fluticasone propionate	25micrograms + 50micrograms/actuation	cfc free inhaler	Inhalation
1258	BECOTIDE 200 aerosol inhaler 200micrograms/actuation [A & H]	beclometasone dipropionate	200micrograms/actuation	aerosol inhaler	Inhalation
35113	beclometasone inhalation powder blisters (refill) 200micrograms	beclometasone dipropionate	200micrograms	inhalation powder blisters (refill)	Inhalation
895	BECLAZONE EASI-BREATHE breath actuated inhaler 100micrograms/actuation [IVAX]	beclometasone dipropionate	100micrograms/actuation	breath actuated inhaler	Inhalation
28073	BECLOMETASONE breath actuated inhaler 250micrograms/actuation [APS]	beclometasone dipropionate	250micrograms/actuation	breath actuated inhaler	Inhalation
27679	BECLOMETASONE breath actuated inhaler 100micrograms/actuation [APS]	beclometasone dipropionate	100micrograms/actuation	breath actuated inhaler	Inhalation
16054	budesonide refillable breath actuated dry powder inhaler 200micrograms/actuation	budesonide	200micrograms/actuation	breath actuated dry powder inhaler	Inhalation
16433	ASMANEX TWISTHALER dry powder inhaler 200micrograms/actuation [SCHERING-P]	mometasone furoate	200micrograms/actuation	dry powder inhaler	Inhalation
26063	BECLOMETASONE aerosol inhaler 100micrograms/actuation [APS]	beclometasone dipropionate	100micrograms/actuation	aerosol inhaler	Inhalation
35107	beclometasone inhalation powder blisters with device 400micrograms	beclometasone dipropionate	400micrograms	inhalation powder blisters with device	Inhalation
36021	fluticasone inhalation powder blisters with device 50micrograms	fluticasone propionate	50micrograms	inhalation powder blisters with device	Inhalation
14321	beclometasone cfc free inhaler 200micrograms/actuation	beclometasone dipropionate	200micrograms/actuation	cfc free inhaler	Inhalation
18394	BDP SPACEHALER 50micrograms/actuation [CELLTECH]	beclometasone dipropionate	50micrograms/actuation	SPACEHALER	Inhalation
35602	budesonide dry powder inhalation cartridge (refill) 200micrograms	budesonide	200micrograms	dry powder inhalation cartridge (refill)	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
14294	QVAR EASI-BREATHE cfc free breath actuated inhaler 50micrograms/actuation [IVAX]	beclometasone dipropionate	50micrograms/actuation	cfc free breath actuated inhaler	Inhalation
14700	budesonide aerosol inhaler 400micrograms/actuation	budesonide	400micrograms/actuation	aerosol inhaler	Inhalation
3570	budesonide refill canister 200micrograms/actuation	budesonide	200micrograms/actuation	refill canister	Inhalation
947	budesonide refill canister 50micrograms/actuation	budesonide	50micrograms/actuation	refill canister	Inhalation
31774	BECLOMETASONE aerosol inhaler 50micrograms/actuation [GEN (UK)]	beclometasone dipropionate	50micrograms/actuation	aerosol inhaler	Inhalation
21482	BECLOMETASONE aerosol inhaler 100micrograms/actuation [GEN (UK)]	beclometasone dipropionate	100micrograms/actuation	aerosol inhaler	Inhalation
34919	BECLOMETASONE aerosol inhaler 50micrograms/actuation [HILLCROSS]	beclometasone dipropionate	50micrograms/actuation	aerosol inhaler	Inhalation
10321	budesonide capsules (for inhalation) 400micrograms	budesonide	400micrograms	capsules (for inhalation)	Inhalation
5975	fluticasone cfc free inhaler 125micrograms/actuation	fluticasone propionate	125micrograms/actuation	cfc free inhaler	Inhalation
5223	fluticasone cfc free inhaler 50micrograms/actuation	fluticasone propionate	50micrograms/actuation	cfc free inhaler	Inhalation
5822	fluticasone cfc free inhaler 250micrograms/actuation	fluticasone propionate	250micrograms/actuation	cfc free inhaler	Inhalation
35986	FLIXOTIDE DISKHALER (REFILL) inhalation powder 50micrograms [A & H]	fluticasone propionate	50micrograms	inhalation powder	Inhalation
39099	PULMICORT cfc free inhaler 100micrograms [ASTRAZENEC]	budesonide	100micrograms	cfc free inhaler	Inhalation
21224	ALVESCO cfc free inhaler 80micrograms/actuation [NYCOMED]	ciclesonide	80micrograms/actuation	cfc free inhaler	Inhalation
5143	SERETIDE 50 EVOHALER cfc free inhaler 25micrograms + 50micrograms/actuation [A & H]	salmeterol xinafoate/ fluticasone propionate	25micrograms + 50micrograms/actuation	cfc free inhaler	Inhalation
3993	FILAIR FORTE aerosol inhaler 250micrograms/actuation [MEDA]	beclometasone dipropionate	250micrograms/actuation	aerosol inhaler	Inhalation
1727	BECOTIDE EASI-BREATHE breath actuated inhaler 50micrograms/actuation [A & H]	beclometasone dipropionate	50micrograms/actuation	breath actuated inhaler	Inhalation
896	BECOTIDE EASI-BREATHE breath actuated inhaler 100micrograms/actuation [A & H]	beclometasone dipropionate	100micrograms/actuation	breath actuated inhaler	Inhalation
99	BECOTIDE 100 aerosol inhaler 100micrograms/actuation [A & H]	beclometasone dipropionate	100micrograms/actuation	aerosol inhaler	Inhalation
34739	BECLOMETASONE aerosol inhaler 50micrograms/actuation [APS]	beclometasone dipropionate	50micrograms/actuation	aerosol inhaler	Inhalation
35430	BECODISKS DISKHALER inhalation powder 200micrograms [A & H]	beclometasone dipropionate	200micrograms	inhalation powder	Inhalation
909	budesonide aerosol inhaler 200micrograms/actuation	budesonide	200micrograms/actuation	aerosol inhaler	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
8433	budesonide aerosol inhaler 100micrograms/actuation	budesonide	100micrograms/actuation	aerosol inhaler	Inhalation
959	budesonide aerosol inhaler 50micrograms/actuation	budesonide	50micrograms/actuation	aerosol inhaler	Inhalation
7891	fluticasone disc 500micrograms	fluticasone propionate	500micrograms	disc	Inhalation
2092	budesonide dry powder inhaler 200micrograms/actuation	budesonide	200micrograms/actuation	dry powder inhaler	Inhalation
7788	budesonide dry powder inhaler 100micrograms/actuation	budesonide	100micrograms/actuation	dry powder inhaler	Inhalation
1642	budesonide dry powder inhaler 400micrograms/actuation	budesonide	400micrograms/actuation	dry powder inhaler	Inhalation
2159	AEROBEC AUTOHALER 50micrograms/actuation [MEDA]	beclometasone dipropionate	50micrograms/actuation	AUTOHALER	Inhalation
4499	AEROBEC forte AUTOHALER 250micrograms/actuation [MEDA]	beclometasone dipropionate	250micrograms/actuation	forte AUTOHALER	Inhalation
1861	AEROBEC AUTOHALER 100micrograms/actuation [MEDA]	beclometasone dipropionate	100micrograms/actuation	AUTOHALER	Inhalation
21005	beclometasone cfc free inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms/actuation	cfc free inhaler	Inhalation
32874	BECLOMETASONE aerosol inhaler 50micrograms/actuation [ACTAVIS]	beclometasone dipropionate	50micrograms/actuation	aerosol inhaler	Inhalation
35652	beclometasone inhalation powder blisters (refill) 100micrograms	beclometasone dipropionate	100micrograms	inhalation powder blisters (refill)	Inhalation
34315	BECLOMETASONE aerosol inhaler 250micrograms/actuation [ACTAVIS]	beclometasone dipropionate	250micrograms/actuation	aerosol inhaler	Inhalation
33258	BECLOMETASONE aerosol inhaler 250micrograms/actuation [HILLCROSS]	beclometasone dipropionate	250micrograms/actuation	aerosol inhaler	Inhalation
9233	beclometasone capsules (for inhalation) 200micrograms	beclometasone dipropionate	200micrograms	capsules (for inhalation)	Inhalation
7653	beclometasone capsules (for inhalation) 400micrograms	beclometasone dipropionate	400micrograms	capsules (for inhalation)	Inhalation
4759	beclometasone capsules (for inhalation) 100micrograms	beclometasone dipropionate	100micrograms	capsules (for inhalation)	Inhalation
1259	beclometasone aerosol inhaler 200micrograms/actuation	beclometasone dipropionate	200micrograms/actuation	aerosol inhaler	Inhalation
10254	mometasone furoate dry powder inhaler 400micrograms/actuation	mometasone furoate	400micrograms/actuation	dry powder inhaler	Inhalation
35288	beclometasone inhalation powder blisters (refill) 400micrograms	beclometasone dipropionate	400micrograms	inhalation powder blisters (refill)	Inhalation
42994	FLIXOTIDE ACCUHALER dry powder inhaler 250micrograms/inhalation [A & H]	fluticasone propionate	250micrograms/inhalation	dry powder inhaler	Inhalation
35611	FLIXOTIDE DISKHALER (REFILL) inhalation powder 250micrograms [A & H]	fluticasone propionate	250micrograms	inhalation powder	Inhalation

pegasus code	Product name	drug substance name	Substance strength	formulation	route
36090	FLIXOTIDE DISKHALER (REFILL) inhalation powder 100micrograms [A & H]	fluticasone propionate	100micrograms	inhalation powder	Inhalation
35700	fluticasone inhalation powder blisters with device 500 micrograms	fluticasone propionate	500 micrograms	inhalation powder blisters with device	Inhalation
34794	BECLOMETASONE aerosol inhaler 200micrograms/actuation [HILLCROSS]	beclometasone dipropionate	200micrograms/actuation	aerosol inhaler	Inhalation
14524	BDP SPACEHALER 250micrograms/actuation [CELLTECH]	beclometasone dipropionate	250micrograms/actuation	SPACEHALER	Inhalation
11198	beclometasone vortex metered dose inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/actuation	vortex metered dose inhaler	Inhalation
15706	beclometasone vortex metered dose inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms/actuatio	vortex metered dose inhaler	Inhalation
9571	beclometasone vortex metered dose inhaler 250micrograms/actuation	beclometasone dipropionate	250micrograms/actuatio	vortex metered dose inhaler	Inhalation
39200	AEROBEC FORTE AUTOHALER 250micrograms/actuation [MEDA]	beclometasone dipropionate	250micrograms/actuatio	AUTOHALER	Inhalation
10090	beclometasone extra fine particle cfc free inhaler 50micrograms/actuation	beclometasone dipropionate	50micrograms/actuation	cfc free inhaler	Inhalation
3150	beclometasone extra fine particle cfc free inhaler 100micrograms/actuation	beclometasone dipropionate	100micrograms/actuation	cfc free inhaler	Inhalation
36290	FLIXOTIDE DISKHALER inhalation powder 50micrograms [A & H]	fluticasone propionate	50micrograms	inhalation powder	Inhalation
9577	ASMABEC CLICKHALER dry powder inhaler 50micrograms [UCB]	beclometasone dipropionate	50micrograms	dry powder inhaler	Inhalation
4601	ASMABEC CLICKHALER dry powder inhaler 100micrograms [UCB]	beclometasone dipropionate	100micrograms	dry powder inhaler	Inhalation
14567	ASMABEC CLICKHALER dry powder inhaler 250micrograms [UCB]	beclometasone dipropionate	250micrograms	dry powder inhaler	Inhalation
7013	SYMBICORT TURBOHALER dry powder inhaler 100micrograms + 6micrograms/actuation [ASTRAZENEC]	budesonide/formoterol fumarate dihydrate	100micrograms + 6micrograms/actuation	dry powder inhaler	Inhalation
6325	SYMBICORT TURBOHALER dry powder inhaler 200micrograms + 6micrograms/actuation [ASTRAZENEC]	budesonide/formoterol fumarate dihydrate	200micrograms + 6micrograms/actuation	dry powder inhaler	Inhalation
1680	PULMICORT LS aerosol inhaler 50micrograms [ASTRAZENEC]	budesonide	50micrograms	aerosol inhaler	Inhalation
3363	BECLOFORTE DISKHALER 400micrograms/actuation [A & H]	beclometasone dipropionate	400micrograms/actuation	DISKHALER	Inhalation
2892	BECLOFORTE disks (refill pack) 400micrograms/actuation [A & H]	beclometasone dipropionate	400micrograms/actuation	disks (refill pack)	Inhalation
35905	fluticasone inhalation powder blisters (refill) 250micrograms	fluticasone propionate	250micrograms	inhalation powder blisters (refill)	Inhalation
35374	FLIXOTIDE DISKHALER (REFILL) inhalation powder 500 micrograms [A & H]	fluticasone propionate	500 micrograms	inhalation powder	Inhalation
33849	BECLOMETASONE aerosol inhaler 100micrograms/actuation [NEOLAB]	beclometasone dipropionate	100micrograms/actuation	aerosol inhaler	Inhalation

Appendix 9. COPD related Read codes

Pegasus code	Read code	Description
11026	9h51.00	Excepted from COPD quality indicators: Patient unsuitable
11266	9h52.00	Excepted from COPD quality indicators: Informed dissent
98283	9kf2.00	COPD structured smoking assessment declined - enh serv admin
11019	8H2R.00	Admit COPD emergency
18717	9h5..00	Exception reporting: COPD quality indicators
18501	66YI.00	COPD self-management plan given
28743	66Yf.00	Number of COPD exacerbations in past year
18476	66YL.11	COPD follow-up
97800	9kf..00	COPD - enhanced services administration
98284	9kf1.00	Refer COPD structured smoking assessment - enhance serv admin
35303	9N4W.00	DNA - Did not attend COPD clinic
19003	66Ye.00	Emergency COPD admission since last appointment
46036	66Yi.00	Multiple COPD emergency hospital admissions
19106	66Yd.00	COPD accident and emergency attendance since last visit
99948	9kf0.00	COPD patient unsuitable for pulmonary rehab - enh serv admin
34202	9Oi1.00	Chronic obstructive pulmonary disease monitoring 2nd letter
34215	9Oi2.00	Chronic obstructive pulmonary disease monitoring 3rd letter
96931	14OX.00	At risk of chronic obstructive pulmonary disease exacerbation
10863	H36..00	Mild chronic obstructive pulmonary disease
10403	14OJ.00	At risk of chronic obstructive pulmonary disease
37247	H3z..11	Chronic obstructive pulmonary disease NOS
37371	66YD.00	Chronic obstructive pulmonary disease monitoring due
10802	H37..00	Moderate chronic obstructive pulmonary disease
42258	9Oi3.00	Chronic obstructive pulmonary disease monitoring verb invite
18792	9Oi..00	Chronic obstructive pulmonary disease monitoring admin
45998	66YT.00	Chronic obstructive pulmonary disease monitoring by doctor
38074	9Oi4.00	Chronic obstructive pulmonary disease monitor phone invite
45771	66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep
19428	1I70.00	Chronic obstructive pulmonary disease excluded by spirometry
45777	8CR1.00	Chronic obstructive pulmonary disease clinic management plan
42313	679V.00	Health education - chronic obstructive pulmonary disease
19567	122D.00	No family history of chronic obstructive pulmonary disease
19434	1J71.00	Suspected chronic obstructive pulmonary disease
93568	H39..00	Very severe chronic obstructive pulmonary disease
26018	66YS.00	Chronic obstructive pulmonary disease monitoring by nurse
18621	66YL.00	Chronic obstructive pulmonary disease follow-up
67040	H3y..11	Other specified chronic obstructive pulmonary disease
9876	H38..00	Severe chronic obstructive pulmonary disease
1001	H3...00	Chronic obstructive pulmonary disease
28755	9Oi0.00	Chronic obstructive pulmonary disease monitoring 1st letter
9520	66YB.00	Chronic obstructive pulmonary disease monitoring
11287	66YM.00	Chronic obstructive pulmonary disease annual review
65733	Hyu3100	[X]Other specified chronic obstructive pulmonary disease
19721	8CE6.00	Chronic obstructive pulmonary disease leaflet given
45770	66Yg.00	Chronic obstructive pulmonary disease disturbs sleep

Appendix 10. Comorbidities used to calculate the Charlson comorbidity score and weighting used

Charlson disease category	Charlson score weight
AIDS	6
Cancer	2
Cerebrovascular disease	1
Chronic pulmonary disease	1
Congestive heart disease	1
Dementia	1
Diabetes	1
Diabetes with complications	2
Hemiplegia	2
Metastatic tumour	6
Mild liver disease	1
Mod liver disease	3
Myocardial infarction	1
Peptic ulcer disease	1
Peripheral vascular disease	1
Renal disease	2
Rheumatological disease	1

Appendix 11. Smoking Read Codes

Med code	Read code	desc	Non smoker	Ex smoker	smoker	Code not used	Passive smoker	passive risk
33	1371.00	Never smoked tobacco	1					
60	137L.00	Current non-smoker	1					
90	137S.00	Ex smoker		1				
93	137P.00	Cigarette smoker			1			
776	137K.00	Stopped smoking		1				
1822	1376.00	Very heavy smoker - 40+cigs/d			1			
1823	137P.11	Smoker			1			
1878	1374.00	Moderate smoker - 10-19 cigs/d			1			
2111	6791.00	Health ed. - smoking				1		
2758	SM7z.11	Smoke inhalation				1		
3568	1375.00	Heavy smoker - 20-39 cigs/day			1			
7130	9OO..12	Stop smoking monitoring admin.				1		
7622	8CAL.00	Smoking cessation advice			1			
9045	ZG23300	Advice on smoking				1		
10184	67A3.00	Pregnancy smoking advice				1		
10211	13p..00	Smoking cessation milestones				1		
10558	137R.00	Current smoker			1			
10560	177..00	Smoke inhalation				1		
10742	8HTK.00	Referral to stop-smoking clinic			1			
10898	13p4.00	Smoking free weeks		1				
11356	9N2k.00	Seen by smoking cessation advisor			1			
11527	9N4M.00	DNA - Did not attend smoking cessation clinic			1			
11788	1371.11	Non-smoker	1					
12240	137G.00	Trying to give up smoking			1			
12619	9hG1.00	Excepted from smoking quality indicators: Informed dissent				1		
12878	137T.00	Date ceased smoking		1				

Med code	Read code	desc	Non smoker	Ex smoker	smoker	Code not used	Passive smoker	passive risk
12941	1372.11	Occasional smoker			1			
12942	137..11	Smoker - amount smoked			1			
12943	137J.00	Cigar smoker			1			
12944	1373.00	Light smoker - 1-9 cigs/day			1			
12946	137F.00	Ex-smoker - amount unknown		1				
12947	137H.00	Pipe smoker			1			
12951	137Q.11	Smoking restarted			1			
12952	137Q.00	Smoking started			1			
12953	9OO1.00	Attends stop smoking monitor.			1			
12955	1379.00	Ex-moderate smoker (10-19/day)		1				
12956	137A.00	Ex-heavy smoker (20-39/day)		1				
12957	1378.00	Ex-light smoker (1-9/day)		1				
12958	1372.00	Trivial smoker - < 1 cig/day		1				
12959	137B.00	Ex-very heavy smoker (40+/day)		1				
12961	1377.00	Ex-trivial smoker (<1/day)		1				
12964	137C.00	Keeps trying to stop smoking			1			
12966	137V.00	Smoking reduced			1			
13350	13WF400	Passive smoking risk						1
13351	137I.00	Passive smoker						1
14694	13WF300	Both parents smoke						1
15714	13WF.11	Smoker in the family						1
16192	13WF200	Mother smokes						1
16717	H310100	Smokers' cough			1			
17437	SM7y200	Smoke inhalation				1		
18573	8H7i.00	Referral to smoking cessation advisor			1			
18926	67H1.00	Lifestyle advice regarding smoking				1		
19485	9OOA.00	Stop smoking monitor.chck done			1			
19488	137O.00	Ex cigar smoker		1				
21637	9OOZ.00	Stop smoking monitor admin.NOS				1		
23017	137U.00	Not a passive smoker				1		
24461	U27..00	[X]Intentional self harm by smoke, fire and flames				1		
26096	13cA.00	Smokes drugs						
26470	137N.00	Ex pipe smoker		1				
27465	13WF100	Father smokes						1
28617	13WF.00	Family smoking history						1
28834	9OO..00	Anti-smoking monitoring admin.				1		
29805	U16..00	[X]Exposure to smoke, fire and flames				1		
30423	137c.00	Thinking about stopping smoking			1			
30644	9hG0.00	Excepted from smoking quality indicators: Patient unsuitable				1		
30762	137d.00	Not interested in stopping smoking			1			
31114	137b.00	Ready to stop smoking			1			
32083	9OO..11	Stop smoking clinic admin.			1			
32356	8I6H.00	Smoking review not indicated				1		
34126	13p0.00	Negotiated date for cessation of smoking			1			
34127	13p1.00	Smoking status at 4 weeks				1		
34374	13p2.00	Smoking status between 4 and 52 weeks				1		
38008	U27z.00	[X]Intent self harm by smoke fire/flames occ unspecif place				1		
38112	13p5.00	Smoking cessation programme start date			1			
40417	9OO3.00	Stop smoking monitor default			1			
40418	9OO2.00	Refuses stop smoking monitor			1			
41042	8CAg.00	Smoking cessation advice provided by community pharmacist			1			
41405	13p3.00	Smoking status at 52 weeks				1		

Med code	Read code	desc	Non smoker	Ex smoker	smoker	Code not used	Passive smoker	passive risk
41979	137e.00	Smoking restarted			1			
42722	9OO4.00	Stop smoking monitor 1st lettr				1		
44827	U47..00	[X]Exposure to smoke, fire and flames, undetermined intent				1		
46321	137f.00	Reason for restarting smoking			1			
47273	ZRaM.00	Motives for smoking scale				1		
49418	ZRh4.11	RFS - Reasons for smoking scale				1		
49512	U16zz00	[X]Exposur unspecif smoke fire/flame occurrn				1		
52148	U470.00	[X]Exposure to smoke fire+flame undeterm intent occ at home				1		
52503	13WK.00	No smokers in the household	1					
53101	9OO7.00	Stop smoking monitor verb.inv.				1		
54481	TD04.00	Smoke NOS from conflagration in private dwelling				1		
54928	U3C..00	[X]Assault by smoke, fire and flames				1		
55199	U16z.00	[X]Exposure to unspecified smoke, fire and flames				1		
57761	13WI.00	Parents do not smoke						
58597	9OO8.00	Stop smoking monitor phone inv				1		
58672	TD14.00	Smoke NOS from conflagration in structure or building				1		
58678	9hG..00	Exception reporting: smoking quality indicators				1		
59866	ZRh4.00	Reasons for smoking scale				1		
60720	9OO5.00	Stop smoking monitor 2nd lettr				1		
63100	U274.00	[X]Intent self harm by smoke fire/flame occ street/highway				1		
63901	9OO9.00	Stop smoking monitoring delete				1		
66387	9OO6.00	Stop smoking monitor 3rd lettr				1		
67791	U16z000	[X]Exposure to unspecifd smoke fire/flames occurrn at home				1		
70373	TD04A00	Smoke NOS from conflagration in tenement				1		
72747	U270.00	[X]Intention self harm by smoke fire/flames occurrn at home				1		
74907	745H.00	Smoking cessation therapy			1			
90522	745Hz00	Smoking cessation therapy NOS			1			
91513	ZRao.00	Occasions for smoking scale				1		
91708	745Hy00	Other specified smoking cessation therapy			1			
93394	U16z200	[X]Exposr unspecif smoke fire/flame sch oth ins/pub adm area				1		
94958	745H400	Smoking cessation drug therapy			1			
96733	TD04500	Smoke NOS from conflagration in house				1		
96992	9kc..00	Smoking cessation - enhanced services administration			1			
97029	137k.00	Refusal to give smoking status				1		
97210	137j.00	Ex-cigarette smoker		1				
97502	13WR.00	Mother does not smoke				1		
97704	U16z600	[X]Exposur unspecif smoke fire/flame occ indust/constr area				1		
98137	67H6.00	Brief intervention for smoking cessation			1			
98154	8HkQ.00	Referral to NHS stop smoking service			1			
98177	9kn..00	Non-smoker annual review - enhanced services administration	1					
98245	8HBM.00	Stop smoking face to face follow-up			1			
98283	9kf2.00	COPD structured smoking assessment declined - enh serv admin				1		

Med code	Read code	desc	Non smoker	Ex smoker	smoker	Code not used	Passive smoker	passive risk
98284	9kf1.00	Refer COPD structured smoking assessment - enhanc serv admin				1		
98347	9ko..00	Current smoker annual review - enhanced services admin			1			
98447	9km..00	Ex-smoker annual review - enhanced services administration		1				
98493	9kc0.00	Smoking cessatn monitor template complet - enhanc serv admin				1		
98640	TD04z00	Smoke NOS from conflagration in private dwelling NOS				1		
99417	U16y000	[X]Exposure to oth specif smoke fire+flames occurrn at home				1		
99838	137K000	Recently stopped smoking		1				
100099	8IAj.00	Smoking cessation advice declined			1			
100495	137l.00	Ex roll-up cigarette smoker		1				
100963	9km..11	Ex-smoker annual review		1				
101069	137I000	Exposed to tobacco smoke at home						1
101210	9NdW.00	Consent given for smoking cessation data sharing			1			
101325	9NdY.00	Declin cons follow-up evaluation after smoking cess interven				1		
101338	137m.00	Failed attempt to stop smoking			1			
101385	9Ndf.00	Consent given for follow-up by smoking cessation			1			
101634	9NdV.00	Consent given follow-up after smoking cessation intervention			1			
101764	13p5000	Practice based smoking cessation programme start date			1			
101851	9Ndg.00	Declined consent for follow-up by smoking cessation team			1			
101854	9NdZ.00	Declined consent for smoking cessation data sharing			1			
101878	9kn..11	Non-smoker annual review				1		
102361	9NS0200	Referral for smoking cessation service offered			1			
102951	13p8.00	Lost to smoking cessation follow-up			1			
103208	13p7.00	Smoking status at 12 weeks				1		
103400	9kf1.11	Referred for COPD structured smoking assessment				1		
33	1371.00	Never smoked tobacco	1					
54	137..00	Tobacco consumption				1		
12954	ZV4K000	[V]Tobacco use				1		
12960	137Z.00	Tobacco consumption NOS				1		
12962	137E.00	Tobacco consumption unknown				1		
12967	137a.00	Pipe tobacco consumption			1			
32687	E251.00	Tobacco dependence				1		
32973	137W.00	Chews tobacco				1		
35055	ZV6D800	[V]Tobacco abuse counselling				1		
37018	6893.00	Tobacco usage screen				1		
42495	68T..00	Tobacco usage screen				1		
43433	SMC..00	Toxic effect of tobacco and nicotine			1			
46654	137D.00	Admitted tobacco cons untrue ?				1		
52189	0C3..00	Tobacco processors				1		
56144	Eu17100	[X]Mental and behav dis due to use of tobacco: harmful use				1		
61905	Eu17.00	[X]Mental and behavioural disorder due to use of tobacco				1		

Med code	Read code	desc	Non smoker	Ex smoker	smoker	Code not used	Passive smoker	passive risk
62686	137h.00	Minutes from waking to first tobacco consumption				1		
67842	0C32.00	Tobacco processor				1		
68658	E251z00	Tobacco dependence NOS				1		
70746	E251100	Tobacco dependence, continuous				1		
72151	0C31.00	Foreman - tobacco processors				1		
72700	ZV11600	[V]Personal history of tobacco abuse				1		
72706	E251300	Tobacco dependence in remission				1		
95610	E251000	Tobacco dependence, unspecified				1		
97973	63C5.00	Maternal tobacco abuse				1		
101069	137I000	Exposed to tobacco smoke at home						1
101519	Eu17300	[X]Mental and behav dis due to use tobacco: withdrawal state				1		
93	137P.00	Cigarette smoker			1			
12945	137M.00	Rolls own cigarettes			1			
12965	137X.00	Cigarette consumption				1		
34814	TDyy400	Accident caused by cigarette				1		
46300	137g.00	Cigarette pack-years				1		
54405	TD3y500	Accident caused by clothes on fire from cigarette				1		
97210	137j.00	Ex-cigarette smoker		1				
100495	137l.00	Ex roll-up cigarette smoker		1				

Appendix 12. Pregnancy codes in CPRD data

ID	pegasus code	read code	read term
95292	127	62...00	Patient pregnant
26656	294	62...11	Antenatal care
26654	13413	62...12	Maternity care
26655	5709	62...13	Pregnancy care
54003	13165	621..00	Patient currently pregnant
91743	4536	621..11	Pregnancy confirmed
58968	16215	6211.00	Pregnant - urine test confirms
52406	30817	6212.00	Pregnant - blood test confirms
59061	35592	6213.00	Pregnant - V.E. confirms
46058	15318	6214.00	Pregnant - on history
67931	51298	6215.00	Pregnant - on abdom. palpation
52343	20240	6216.00	Pregnant - planned
74202	14842	6217.00	Pregnant - unplanned - wanted
93549	15567	6218.00	Pregnant -unplanned-not wanted

Appendix 13. BMI codes in CPRD data

medcode	readcode	desc	Result for…
8105	22K..00	Body Mass Index	Body mass index
9015	22K4.00	Body mass index index 25-29 - overweight	Body mass index
13278	22K5.00	Body mass index 30+ - obesity	Body mass index
22556	22K7.00	Body mass index 40+ - severely obese	Body mass index
24496	22K6.00	Body mass index less than 20	Body mass index
28937	22K2.00	Body Mass Index high K/M2	Body mass index
28946	22K1.00	Body Mass Index normal K/M2	Body mass index
32914	22K3.00	Body Mass Index low K/M2	Body mass index
44291	22K8.00	Body mass index 20-24 - normal	Body mass index
101047	22K9.00	Body mass index centile	Body mass index

medcode	readcode	desc	Result for…
2	22A..00	O/E - weight	weight
2839	22A4.11	O/E - overweight	weight
3355	66C9.11	Weight loss advised	weight
6713	8CA4011	Patient advised to lose weight	weight
8304	ZC2C711	Dietary advice for weight reduction	weight
8481	66CC.00	Wants to lose weight	weight
8964	8B57.00	Weight reducing diet	weight
9015	22K4.00	Body mass index index 25-29 - overweight	weight
11443	ZC1..00	Actions to lose weight	weight
11763	ZC2C700	Patient advised about weight-reducing diet	weight
12445	ZG53100	Patient advised to lose weight	weight
13076	13A3.00	Weight reducing diet	weight
13078	13AC.00	Diabetic weight reducing diet	weight
16404	22A4.00	O/E - weight 10-20% over ideal	weight
21520	22AZ.00	O/E - weight NOS	weight
22343	ZC17.00	Exercising to lose weight	weight
26351	1626.00	Intentional weight loss	weight
29721	66CD.00	Difficulty maintaining weight loss	weight
32974	22A5.00	O/E - weight > 20% over ideal	weight
43375	ZC2CO00	Dietary advice for weight loss	weight
43806	ZC1A.00	Excessive exercising to lose weight	weight
102150	66CM.00	Risk health associ overweight and obesity, at increased risk	weight
102514	66CN.00	Risk health associated overweight and obesity, at high risk	weight
3	229..00	O/E - height	height
41045	229Z.00	O/E - height NOS	height
57111	22Z..00	Height and Weight	height

Appendix 14. Adverse effects of ICS Read codes, the presence of oral thrush, osteoporosis or adrenal suppression in CPRD data.

Oral Thrush

medcode	readcode	desc
196	AB20011	Oral thrush
5939	AB20.12	Thrush of mouth and oesophagus

Osteoporosis

medcode	readcode	desc
277	N330.00	Osteoporosis
3346	N330B00	Vertebral osteoporosis
4013	N331L00	Collapse of vertebra due to osteoporosis NOS
5841	N331J00	Collapse of lumbar vertebra due to osteoporosis
9700	N330200	Postmenopausal osteoporosis
10293	66a0.00	Initial osteoporosis assessment
10359	66a1.00	Follow-up osteoporosis assessment
11218	1268.00	FH: Osteoporosis
11503	N331M00	Fragility fracture due to unspecified osteoporosis
11603	66a..00	Osteoporosis monitoring
12673	N331900	Osteoporosis + pathological fracture thoracic vertebrae
13055	679F.00	Health education - osteoporosis
14967	N330000	Osteoporosis, unspecified
16307	N330100	Senile osteoporosis
16857	N330C00	Osteoporosis localized to spine
17045	1229.00	No FH: Osteoporosis
17377	N331800	Osteoporosis + pathological fracture lumbar vertebrae
18265	9N0h.00	Seen in osteoporosis clinic

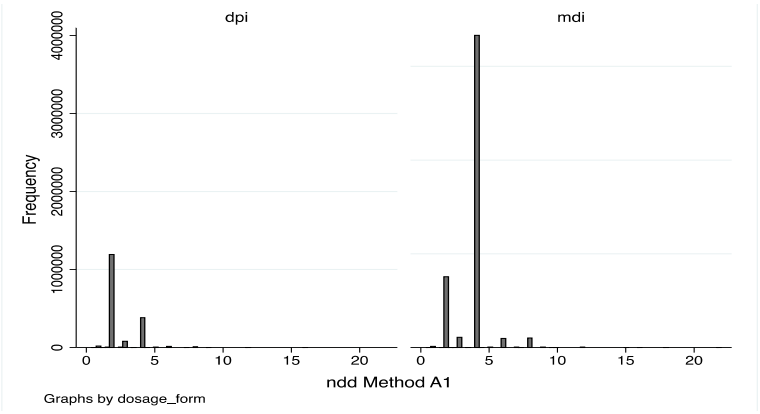
medcode	readcode	desc
18825	NyuB800	[X]Unspecified osteoporosis with pathological fracture
19048	N331K00	Collapse of thoracic vertebra due to osteoporosis
24093	N330500	Drug-induced osteoporosis
25534	9Od9.00	Osteoporosis monitoring check done
25650	N330D00	Osteoporosis due to corticosteroids
26292	66a9.00	Osteoporosis - falls prevention
26876	66a6.00	Osteoporosis - dietary advice
27597	N331600	Idiopathic osteoporosis with pathological fracture
28882	8HTS.00	Referral to osteoporosis clinic
31580	N330A00	Osteoporosis in endocrine disorders
33526	N331300	Osteoporosis of disuse with pathological fracture
34129	66a4.00	Osteoporosis treatment changed
34798	N330z00	Osteoporosis NOS
36644	66a3.00	Osteoporosis treatment stopped
37646	66a2.00	Osteoporosis treatment started
38395	N331B00	Postmenopausal osteoporosis with pathological fracture
38903	66a7.00	Osteoporosis - dietary assessment
39334	N331200	Postoophorectomy osteoporosis with pathological fracture
39596	66aE.00	Refer to osteoporosis specialist
40428	N330300	Idiopathic osteoporosis
41376	66a8.00	Osteoporosis - exercise advice
41755	NyuB100	[X]Other osteoporosis
45274	9Od1.00	Refuses osteoporosis monitoring
45736	N331H00	Collapse of cervical vertebra due to osteoporosis
46894	N331500	Drug-induced osteoporosis with pathological fracture
48772	N331A00	Osteoporosis + pathological fracture cervical vertebrae
48962	66a5.00	Osteoporosis - no treatment
54232	N330800	Localized osteoporosis - Lequesne
57301	NyuB000	[X]Other osteoporosis with pathological fracture
60433	N330900	Osteoporosis in multiple myelomatosis
62702	N330400	Dissuse osteoporosis
68019	N331400	Postsurgical malabsorption osteoporosis with path fracture
68122	9Od3.00	Osteoporosis monitoring first letter
70233	66aA.00	Osteoporosis - treatment response
70349	N330600	Postoophorectomy osteoporosis
89922	8I6c.00	Osteoporosis treatment not indicated
92887	9Od2.00	Osteoporosis monitoring default
93455	9Od4.00	Osteoporosis monitoring second letter
93655	N330700	Postsurgical malabsorption osteoporosis
93705	N331M11	Minimal trauma fracture due to unspecified osteoporosis
96779	9Od8.00	Osteoporosis monitoring deleted
98189	66aB.00	Osteoporosis - no treatment response
98433	9kj..00	Osteoporosis - enhanced services administration
98760	9kj0.00	Bone sparing drug treatment offered for osteoporosis - ESA
99817	14GB.00	History of osteoporosis
101068	8B6b.00	Osteoporosis medication prophylaxis
101386	2126500	Osteoporosis resolved
101443	9hP0.00	Excepted osteoporosis quality indicators: patient unsuitable
102017	9Od5.00	Osteoporosis monitoring third letter
102169	9hP..00	Exception reporting: osteoporosis quality indicators
102730	NyuB200	[X]Osteoporosis in other disorders classified elsewhere

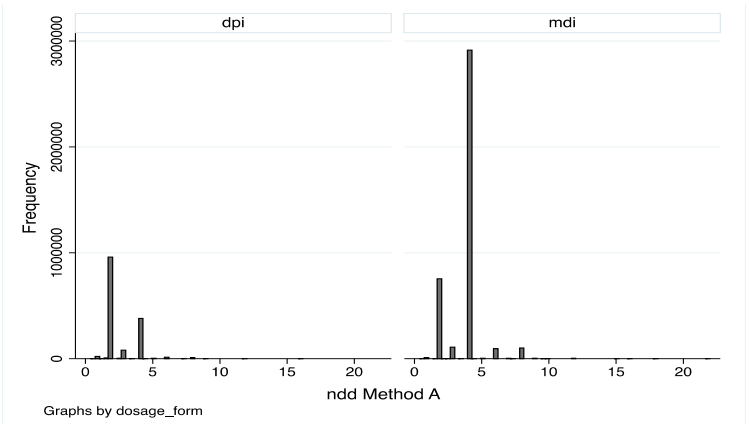
Adrenal suppression/ insufficiency

ID	medcode	readcode	desc
3114	3113	C154.00	Corticoadrenal insufficiency
8783	8782	C155.00	Other adrenal hypofunction
12397	12396	C154z00	Corticoadrenal insufficiency NOS
12877	12876	C15..00	Disorders of adrenal glands
20787	20786	C154z12	Adrenal insufficiency NEC
21540	21539	C154000	Acute adrenal insufficiency
25293	25292	PK1..00	Anomalies of adrenal gland
28897	28896	C154z11	Adrenal hypofunction
29819	29818	PK13.00	Hypoplasia of adrenal gland
36065	36064	PK1z.00	Anomalies of adrenal gland NOS
41543	41542	C15z.00	Adrenal gland disorder NOS
42874	42873	C154012	Adrenal crisis
44419	44418	C15yz00	Other specified adrenal disorder NOS
54839	54838	C155z00	Other adrenal hypofunction NOS
56390	56389	C15y.00	Other specified adrenal disorders
63825	63824	PK1y.00	Other specified anomalies of adrenal gland
73530	73529	C155000	Adrenal medullary insufficiency
99224	99223	Cyu4A00	[X]Other specified disorders of adrenal gland

Appendix 15. NDD dosage form assumptions

To justify the NDD assumption of 2 for dpi and 4 for mdi, The histograms below illustrate this These clearly show that the majority of the NDD's for each prescription are 2 for dpi and 4 for mdi., however the graphs also show a second value for each category, but is much less common than the chosen values.





Appendix 16. Read coded exacerbation events

Pegasus code	read code	Description	Primary or secondary care
232	H33z100	Asthma attack	1
185	H333.00	Acute exacerbation of asthma	1
18323	H331111	Intrinsic asthma with asthma attack	1
8335	H33z111	Asthma attack NOS	1
6707	H330111	Extrinsic asthma with asthma attack	1
41020	66YC.00	Absent from work or school due to asthma	1
28297	663a.00	Oral steroids used since last appointment	1
29060	663F.00	Oral steroids started	1
7534	2324.00	O/E - respiratory distress	1
47337	663m.00	Asthma accident and emergency attendance since last visit	2
233	H33z011	Severe asthma attack	2
7058	8H2P.00	Emergency admission, asthma	2
24479	663d.00	Emergency asthma admission since last appointment	2
51448	9NW0.00	Seen by rapid response team - respiratory	2
55029	7459.00	Other respiratory support	2
25249	H59..00	Respiratory failure	2
3959	R2y1.00	[D]Respiratory failure	2
2563	R060600	[D]Respiratory distress	2
15779	R2y1z00	[D]Respiratory failure NOS	2
67786	8H12.00	Admit to respiratory ITU	2
25703	8H7j.00	Referral to respiratory rapid response team	2
37961	H590.00	Acute respiratory failure	2
3961	R2y1100	[D]Respiratory arrest	2

Appendix 17. Variables included in the analysis

category	Variable	Time dependent	Description of the data		Variable type (number of categories)	Statistical test for adherence comparison	Variable name
Patient identifier	**Patient identification number**		Unique anomalised identification number		Panel variable		patid
time variables	**Years in study**	yes	The number of years since the patient first met the inclusion criteria for the study		continuous		year_number
	Calendar year		The calendar year when each variable was measured		continuous		yr
	Year since first SABA prescription (in data)	yes	The number of years since the patients first recorded SABA prescription		continuous		Yr_first_SABA
Adherence	**Adherence**	yes	Recorded as a % of days with medicine prescribed over the year, censored at 100%		continuous		PPR_censored
Social and economic	**Gender**	no	0=male 1=female (2= intermediate		Dummy	Wilcoxon-Mann_Whitney test	gender_dummy
	Marital status	no	0=Data Not Entered 1=Single 2=Married 3=Widowed 4=Divorced 5=Separated A grouped variable was also created to group the main categories (1)married= married or re married (2)separated= widowed, divorced or separated (3)single=single (4)relationship= cohabiting or stable relationship	6=Unknown 7=Engaged 8=Co-habiting 9=Remarried 10=Stable relationship 11=Civil Partnership	categorical	Kruskal Wallis test	marital
	Region of living	no	Based on the Strategic Health Authority where the patient is registered 0=Data Not Entered 1=North East 2=North West 3=Yorkshire & The Humber 4=East Midlands 5=West Midlands 6=East of England	7=South West 8=South Central 9=London 10=South East Coast 11=Northern Ireland 12=Scotland 13=Wales	categorical	Kruskal Wallis test	region
	Socioeconomic status	no	The SES for where the patient lives, 1= least deprived, 5=most deprived		Categorical,	Spearman rank	

category	Variable	Time dependent	Description of the data	Variable type (number of categories)	Statistical test for adherence comparison	Variable name
				ordinal		
	Age in years	Yes	The age of the patient based on a birth date of January 1 in the recorded year of birth 1:>=12 to <19 2:>=20< to 25 3:>=26< to 35 4:>=36 to -<45 5:>=46 to <55 6:>=56 to -<65	Categorical, ordinal	Spearman rank	age
Patient factors	**Comorbidities**	no	The patients charlson cormorbidity score based on the data available up to 2007, scored from 1- 18.	Categorical, ordinal	Spearman rank	Charlsoton_1997
	Smoking status	no	0= nonsmoker 1= ever smoked Or, 0= nonsmoker 1= smoker 2= ex-smoke 3= passive smoke missing= data not entered	Dummy categorical	Wilcoxon-Mann_Whitney test n/a	smoker/ smoking_status
	Prescription exemption	no	0=no exemption, 1= exemption	dummy	Wilcoxon-Mann_Whitney test	exemption
	BMI	yes	Categorised where available into underweight=0, ideal=1 or overweight=2	categorical	Kruskal Wallis test	round_BMI
	Pregnancy	yes	A year where a patient has a code for 1=pregnancy 0= no record	dummy	Wilcoxon-Mann_Whitney test	pregnant
therapy related factors	**Adverse effects from ICS/OCS**	yes	An indicator for whether the patient has experienced oral thrush, osteoporosis or adrenal suppression during the year (1= experiences at least once during the year)	dummy	Wilcoxon-Mann_Whitney test	oral_thrus~n, osteoporos~n, adrenal_supression~n
	Type of ICS device	yes	Whether the patient has been prescribed a 1=MDI 2=DPI 3= both	categorical	Kruskal Wallis test	MDI
	Drug substance	yes	A dummy variable for whether each drug substance had been prescribed. beclometasone, budesonide, ciclesonide, mometasone, fluticasone	dummyl	Wilcoxon-Mann_Whitney test	beclometasone, budesonide, ciclesonide, mometasone, fluticason~n
condition related variables	**Severity of Asthma Indicator of asthma severity by treatment step.**	yes	Recorded as step 2 to 5 (set as 1-4 representing 2-5)	Categorical, ordinal	Spearman rank	treatment_step

category	Variable	Time dependent	Description of the data	Variable type (number of categories)	Statistical test for adherence comparison	Variable name
	Change in step from previous year	yes	Recorded as + or – the number of years from the previous year	continuous	n/a	stepchange
	Control of asthma symptoms by	yes	0= patient has received prescriptions for under 10 SABA per day 1=patient has received prescriptions for10 or more SABA per day	dummy	Wilcoxon-Mann_Whitney test	over_10
	Annual total Asthma exacerbations	yes	The number of asthma exacerbations treated within primary or secondary care. Also converted to a dummy variable (1=the patient has been treated at least once in the year for an asthma exacerbation)	continuous	n/a	all_exac_pa
	Secondary care exacerbation	yes	A recorded asthma exacerbation requiring a hospital admission (1=the patient has been admitted at least once in the year for asthma exacerbation)	dummy	Wilcoxon-Mann_Whitn ey test	Secondary_exac_dumm y
	Primary care exacerbation	yes	A recorded asthma exacerbation treated within primary care (1=the patient has been treated within primary care at least once in the year for asthma exacerbation)	dummy	Wilcoxon-Mann_Whitn ey test	primary_exac_dummy/

Appendix 18. High PPR values example explanations

There is an extremely high PPR result for 1 year (2009) for an individual patient. The patient left the study data on the 15th of Jan after receiving 4 prescriptions (853 days of medicine).

There is also a high PPR result for 1 year (2010) for another patient since the patient also left the study data on the 14th of Jan after receiving 2 prescriptions and 365 doses passes from the previous year (765 days of medicine).

Appendix 19. Variables used in the model

Independent variable type	**Variables and Lagged variables**	**Variable working name**		**Analysis 1**	**Analysis 2**	**Analysis 3**	
Endogenous variables used as a GMM instrument	PPR persistence (for past 2 years)	L(1/2).PPR_A2_censored	dummy	✓	✓	✓	
	Exacerbation occurrence- any severity	all_exac_pa_dummy	dummy	x	✓	x	
	Total exacerbations in current year	all_exac_pa	continuous	✓	x	✓	
	Exacerbation occurrence in previous year- treated within primary care	L.primary_exac_pa_dummy	dummy	✓	✓	✓	
	Exacerbation occurrence in previous year- treated within secondary care	L.secondary_exac_pa_dummy	dummy	✓	✓	✓	
	The interaction between the occurrence of an exacerbation treated within primary and secondary care	L.interact*	dummy	✓	✓	✓	
Strictly exogenous	Patient age	Age/ aged	Continuous/ categorical	✓	✓	✓	
	Control by SABA use	over_10		✓	✓	✓	
	Year since entering study	year_number	dummy	✓	✓	✓	
	Treatment step	i.final_step	continuous	✓	✓	✓	
	Change in treatment step	stepchange	categorical	✓	✓	✓	
	Smoking status	Smoker	categorical	x	x	✓	
	BMI		continuous	x	x	✓	
	Type of ICS device		dummy	x	x	✓	
	ICS Drug substance		Entered as individual variables	x	x	✓	
	Pregnancy indicator		dummy	x	x	✓	
	Comorbidity score		continuous	x	x	✓	
Time invariant	Gender		time invariant	✓	✓	✓	
	Marital Status		time invariant	x	x		
	Region of living		time invariant	x	x		
	Prescription exemption		time invariant	x	x		
Weakly (predetermined) exogenous variables	??						

Options- side effects, year since first treatment with SABA recorded, SES

Appendix 20. The STATA syntax

```
xtabond2 [dependent variable] [all explanatory
variables] /// i.[categorical explanatory variables]
///
if [time invariant variable==1], twostep robust small
```

A number of options were also included in the syntax:

twostep-computes the two step rather than the 1 step estimator

robust- If two step has been selected, this option selects Windmeijer's finite-sample correction for the two step covariate matrix.

small- requests the t statistics instead of the z statistics and an F test instead of a Wald chi-squared test of overall model fit.

Appendix 21 Summary of cohort characteristics used in Analysis 1 and 2 in Chapter 8

			Study cohort				Analysis 1(n=658178 patients)			Analysis 2(n=276805 patients)		
Variable name and definition		**Variable type**	**Obs (N)**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**
Adherence to ICS (PPR)		continuous	822494	67.56	0.46	100	70.22	0.72	100	70.67	0.72	100
The year that the variables are measured		continuous	822494	2005	1997	2010	2005	1998	2010	2006	1997	2010
Gender		dummy	822494	0.57	0	1	0.57	0	1	0.61	0	1
Socioeconomic status		categorical	817657	3	1	5	3	1	5	3	1	5
Comorbidities		dummy	822494	0.34	0	1	0.38	0	1	0.37	0	1
Co- payment exemption		dummy	822494	0.34	0	1	0.20	0	1	0.18	0	1
Patient Characteristics												
Age in years		categorical	822494	4	1	6	4	1	6	4	1	6
Smoking status (ever smoked)		dummy	578413	0.6	0	1	0.7	0	1	0.5	0	1
Drug substance	**beclometasone**	dummy	822494	0.63	0	1	0.60	0	1	0.56	0	1
	budesonide	dummy	822494	0.16	0	1	0.17	0	1	0.18	0	1
	ciclesonide	dummy	822494	0.002	0	1	0.001	0	1	0.002	0	1
	mometasone	dummy	822494	0.002	0	1	0.002	0	1	0.002	0	1
	fluticasone	dummy	822494	0.28	0	1	0.30	0	1	0.35	0	1
Pregnancy		dummy	822494	0.01	0	1	0.01	0	1	0.01	0	1
Secondary care exacerbation		dummy	822494	0.01	0	1	0.20	0	1	0.22	0	1
Primary care exacerbation		dummy	822494	0.2	0	1	0.01	0	1	0.01	0	1
Treatment step (set as 1-4 representing 2-5)		categorical	822949	1.83	1	4	1.88	1	4	1.92	1	4
Change in step from previous year		continuous	788248	0.04	-3	3	0.04	-3	3	0.06	-3	3
Greater than 10 doses of SABA per day		dummy	822949	0.05	0	1	0.06	0	1	0.06	0	1
Years in study		continuous	822949	6.58	1	14	4.36	1	14	4.71	1	14

Appendix 22 Summary of results from Chapters 6 to 9

			Adherence			Clinical outcome	
			2 way analysis	Modelling of adherence		2 way analysis- the effect on clinical outcome	
	Variable name	Variable subgroups	PPR lower with.	Lower PPR associated with	Lower PPR with the following subgroups	Higher risk of primary care exacerbation associated with	Higher risk of secondary care exacerbation associated with
	Years in study	1-14	Fewer years	Fewer years	n/a	More years in study	Fewer years in study
Patient	Gender	Male	Female	Females	Fluticasone / budesonide prescribed, increase in step, more years in study		
		Female			Treated at higher step, primary care exacerbation, smoker, ciclesonide prescribed, poor control		
	Age in years		Younger age	Younger age	n/a		
	Comorbidities	No Comorbidity	Fewer comorbidities	No comorbidities	Treated at step 5, decrease in treatment step, primary care exacerbation		
		>1 Comorbidity			Poor control, fluticasone/ budesonide prescribed, treated at step 3 /4, poor control, increased step		
	Smoking	Ever smoked=1	Non-smoker	Non-smoker	n/a		
	Pregnancy	Pregnant=1	Pregnant	Not significant	n/a		
Deprivation	Deprivation	Most deprived	Least deprived	Least deprived	Treated at step 3 and 4, fluticasone / budesonide prescribed, smoker, poor control		
		Least deprived			Ciclesonide prescribed, more years in study		
	Prescription exemption	Exempt	Non exemption	Exempt	Primary care exacerbation (previous year), budesonide prescribed, smoker		
		Non exempt			Treatment step higher than 2, fluticasone /ciclesonide prescribed, poor control, increase in step		
Therapy	Drug substance		Mometasone/ fluticasone	Fluticasone	n/a		
	Adherence	Previous year	n/a	Low PPR	n/a		
		2 years previous	n/a	Low PPR	n/a		
Condition	Severity of Asthma	2-5	Lower treatment step	Higher treatment step	n/a	More severe asthma	More severe asthma
	Change in step	-3 to +3	No change, then decrease	Decreased step	n/a	Increase in step	n/a
	Poor control		Good control	Good control	n/a	Poor control	n/a
	Primary care exacerbation	Same year	No exacerbation	Exacerbation	n/a		
		Previous year	No exacerbation	No exacerbation	n/a		
	Secondary care Exacerbation	Same year	Not significant	Not significant	n/a		
		Previous year	Not significant	No exacerbation	n/a		

Appendix 23 **Peer reviewed paper**

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RESEARCH ARTICLE

Adherence to inhaled corticosteroids by asthmatic patients: measurement and modelling

Amelia Taylor · Li-Chia Chen · Murray D. Smith

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Abstract *Background* Poor adherence to inhaled corticosteroids (ICS) is known as the main cause for therapeutic failure in asthma treatment and associated morbidity. To improve adherence, targetted and effective interventions need to be developed ideally based on using longitudinal follow-up of a large study cohort to establish patterns and influences on adherence. *Objective* To develop an annual measure of asthma patients' adherence to ICS using primary care prescribing data over consecutive annual intervals, and to statistically model ICS adherence controlling for a range of patient factors. *Setting* A retrospective cohort study between 1997 and 2010 using United Kingdom general practice prescribing data on asthma patients aged between 12 and 65 years, without a diagnosis of chronic obstructive pulmonary disease. *Method* Patient's ICS prescriptions are used to calculate the 'number of days prescribed during calendar year' divided by 'number of days in the interval' to form an annual prescription possession ratio (PPR) for each patient. Several definitions of PPR are considered and compared when calculating numerator and denominator. Adherence, measured by the preferred PPR, is then modelled to estimate the effect of asthma exacerbation, severity, control and other patient factors on adherence. *Main outcome measure* PPR, being a proxy measure for adherence. *Results* Annual PPR by all strategies gave a similar frequency profile. ICS were either over- or under-prescribed for over half of the follow-up time. Adherence was lower in younger patients, those newer to the study timeframe, those with less severe asthma, those with good control, with lower previous adherence, and who had not previously experienced an exacerbation. *Conclusion* The chosen PPR simulated clinical use of ICS most closely; including overlapping days, excess days passed to the next interval, considering gaps in the denominator, with censoring at 100 %. The PPR is a useful measure for signalling or measuring adherence changes over time. The modelling results identified many characteristics which would indicate which asthma patients and at what points in their treatment cycle they would be at increased risk of low adherence.

Keywords Adherence · Asthma · Exacerbation · Panel data · Prescription possession ratio

A. Taylor · L.-C. Chen · M. D. Smith (✉)
Division for Social Research in Medicines and Health, School of Pharmacy, The University of Nottingham, University Park, Nottingham NG7 2RD, UK
e-mail: murray.smith@nottingham.ac.uk

Impact of findings on practice statements

- A method to measure adherence has been developed for use with ICS in asthma patients, which could be used in other retrospective adherence studies or in clinical practice to monitor patients' adherence.
- Modelling methodology has begun to identify risk factors that could be used to target asthma patients at risk of poor adherence to ICS, which could be used to identify and target efficient and effective interventions to improve adherence.

Introduction

Medication adherence is commonly defined as: "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [1]. Non-adherence to medicine is associated with reduced health outcomes

[2–4] and is a notable issue for long-term conditions as non-adherence rates for long-term therapy typically exceed 50 % [5–7]. A better understanding of the patterns of change in adherence over time and the factors that may contribute to poor adherence is especially important in the management of long term chronic conditions. In order to elicit these patterns and influences, longitudinal follow-up and large sample sizes are needed to facilitate the necessary statistical analyses. Outcomes from such work will contribute to the development of efficient adherence-promoting interventions targeted at the most appropriate times in a patient's treatment cycle.

Currently, there is no gold standard measure of adherence. Approaches to measurement include pill counts, electronic measuring devices, patient log books etc. These may be suitable in small clinical trials but are impractical and overly expensive for monitoring medicine use during routine care, or across large samples of patients. Dispensing data administratively linked to medical records have been used in some studies [8] but in the UK such data are not available in sufficiently large samples. Alternately, patient-level primary care prescribing data can be used to generate a prescription possession ratio (PPR), defined as the proportion of the combined number of days prescribed by individual prescriptions over an annual interval as part of a patient's long term treatment. PPR can be considered a proxy measure for adherence under the assumption that a patient will fill prescriptions and take the medicine. However, prescribing frequency and quantity are affected by both patient attendance at a doctor's appointment to be able to receive the prescription (or to request a repeat prescription) and the prescribers choice to write the prescription. Despite these limitations, evidence from a New Zealand study (n = 646) found that adherence estimated using prescription data was "a useful predictor of dispensing-based adherence" [9].

For asthma management, although the evidence-based effectiveness of asthma medicines has been proven and clear prescribing guidelines are available [10, 11], adherence to asthma medicines is known to be low; for example, Andersson et al. [12] found refill-adherence for asthma medicines one of the lowest (34 %) when compared to treatments for other long-term conditions.

In this study, we focussed on inhaled corticosteroids (ICS) because adherence by asthmatics to these medicines has been reported to be especially poor [13] and has been identified as the main cause for failure in asthma treatment [14] with consequences that include increases in asthma exacerbations, decreases in patient quality of life [6], and increases in morbidity, mortality and healthcare costs to the UK's National Health Service [15, 16]. The effect of different factors on adherence were considered, including the age of the patient, control of symptoms, severity of asthma, and whether the patient had experienced an asthma exacerbation.

Aim of the study

First, to develop an annual measure of asthma patients' adherence to ICS by using UK primary care prescribing data over consecutive annual intervals; and second, to construct and estimate a patient-level statistical model of ICS adherence controlling for a range of individual patient factors.

Methods

Study design and cohort

This retrospective cohort study used data extracted from the Clinical Practice Research Datalink (CPRD) database [17]. CPRD is a longitudinal database containing anonymised medical records on approximately 12.5 million acceptable patients (December 2012 build) registered across 661 general practices located throughout the UK (April 2013 build). Included in the study were asthma patients aged between 12 and 65 years whose records in CPRD fell within the study period 1997–2010 and who were consented for administrative linkage to their hospital episode statistics (HES) secondary care inpatient records, and who were without chronic obstructive pulmonary disease (COPD). Patients were followed from their respective index date (when the patient met the inclusion criteria for entry into the sample frame) up until either: (a) the end date of the study, or (b) when they reached their 65th birthday, or (c) were diagnosed with COPD, or (d) died or were transferred out of their GP practice. Approval for the study was granted by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (protocol number 13_036R).

Data management

Included patients' ICS prescriptions were collected and the prescribing date and duration (number of days prescribed) were then used to calculate PPR. Missing values for prescribing duration were imputed by calculating the number of doses prescribed (quantity of packs multiplied by its number of doses) divided by the recorded daily prescribed dose. Errors (such as duplications, swaps, or missing values) in the number of doses in the pack (pack type) were checked and any outlying values were corrected based on pack information taken from the British National Formulary [18]. Missing values for the daily prescribed dose were

imputed using the patient's prior prescription records or, if unavailable, by substitution of the sample median of the daily prescribed dose by dosage form.

Asthma exacerbation and severity of asthma

Asthma exacerbations were distinguished by whether they were hospital-recorded (the primary diagnosis ICD-10 coding in HES episode data was J45 or lower) or were managed in primary care (identification of oral prednisolone use to treat exacerbation in the CPRD therapy file). In addition, keywords ("asthma" and "exacerbation", "emergency prednisolone", "admit to hospital", etc) were matched with relevant Read codes to identify occurrences of them in the CPRD clinical file, which were then classified as exacerbation treatment within primary or secondary care.

To identify oral prednisolone prescribing to treat an exacerbation, criteria considering the duration (less than 10 days per prescription, less than 90 days per year) and quantity/dose (qty of less than or equal to 20 and strength is 25 mg, or qty of less than or equal to 112 and strength is 5 mg) were used. Any patient-years with a prednisolone prescription which failed to meet these criteria were not considered to be indicative of an exacerbation. Instead, these patient-years were classified as being treated within step 5 of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines [11]. These guidelines are such that a patient's asthma severity is increasing in treatment step (ranging from steps 1 to 5) where additional medicines or higher doses are required to achieve control. A patient presenting at step 1 has their asthma controlled with a short-acting β_2-agonist (SABA) alone, whereas a step 5 patient requires routine daily prednisolone treatment in order to control their asthma.

Measuring adherence

In this study, a patient's adherence to ICS prescriptions was measured using PPR. This was calculated by dividing 'number of days prescribed during calendar year' by 'number of days in the interval' and thus was the proportion of days in the year where medicine was prescribed [8]. Expressed as a percentage, it was constructed as follows:

$$PPR = 100 \times \frac{\text{Number of days prescribed during calendar year}}{\text{Number of days in the interval}}$$

Several approaches were considered when evaluating the numerator, distinguished by whether or not to include or exclude the overlap in prescription days, and whether to pass excess prescription days over to the next interval or to share these proportionally between intervals (see Fig. 1). The denominator was set to 365 days for an annual interval, but was adjusted at the beginning or end for when a patient entered or left the follow-up, or for missing data in number of doses.

By combining these approaches in differing ways, four possible strategies were defined for calculating PPR (see top half of Table 1), of which the first—strategy 1 (including overlapping days, passing excess days to the next interval, and adjustments to the beginning and end intervals)—represents the base case. A fifth strategy imposed a censoring rule on the base case, namely, any computed value of PPR that exceeded 100 % is reset to 100 %. PPR was calculated for each patient annually using each strategy (1–5) and the results presented descriptively.

Modelling adherence

Prescription possession ratio serves as a proxy variable for adherence (we denote adherence by A and note that it is unobservable) and so it is subject to error when using it as a measure of adherence. Let the relationship between these variables be:

$$PPR = A + U$$

where the unobservable error term U is assumed to have zero mean. We constructed and estimated inferential models designed to explain adherence A in terms of its dynamic behaviour through time as well as to demonstrate its relationship to clinical outcomes and other factors. In particular, we use a panel data model to match the study's data structure (unbalanced panel data) and consider fixed effects representations, for example:

$$PPR_{it} = \alpha PPR_{i,t-1} + \gamma Y_{it} + \beta_0 + \beta_1 X_{1it} + \cdots + \beta_k X_{kit} + \lambda_i + U_{it}$$

where indexes $i = 1, \ldots, N$ patients and $t = 1, \ldots, T$ time periods. The unknown coefficients to be estimated include: α the coefficient of the lagged dependent variable PPR_{-1} designed to capture any dynamic relationships adherence may have with itself over time; γ the coefficient of Y that represents clinical outcome and which arguably has a feedback causal effect with adherence; $(\beta_0, \beta_1, \ldots, \beta_k)$ as the set of $k+1$ coefficients on a set of independent regressors $(1, X_1, X_2, \ldots, X_k)$ where 1 denotes the intercept and $(X_1, X_2, \ldots, X_k)$ are patient-measured attributes (see Table 2). The patient-specific, arbitrarily distributed individual fixed effect is represented by λ. The error term U can be heteroscedastic and autocorrelated. This type of panel data model has been extensively studied and applied in numerous studies [19–21]. System generalised method of moments (system GMM) is an appropriate estimator for

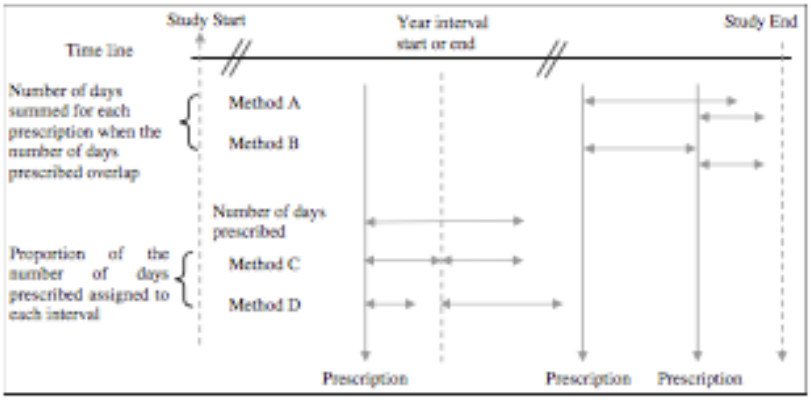


Fig. 1 Calculating the PPR numerator when prescription supply overlaps or when the prescription cuts across the interval start or end

Table 1 Descriptive statistics

PPR strategy[a]		Patient-years (total = 824,943)	Mean	SD	Min	Max	Median
1	A, C, E	822,503	85.45	71.51	0.46	6,135.71	69.86
2	B, C, E	822,503	61.52	27.02	0.36	100	61.92
3	A, D, E	662,797	87.86	67.37	0.36	4,718.52	73.47
4	C, C, F	822,526	80.23	58.28	0.82	1,362.74	66.3
5	Censored strategy 1 at 100 %	822,503	57.56	28.92	0.46	100	69.86
Patient characteristics							
	Age in years		38.72	15.41	12	65	39
	Years in study		3.90	2.96	1	14	3
	SABA use		0.04	0.19	0	1	0
	BTS/SIGN step		2.70	0.85	2	5	2
	Annual change in step		0.02	0.45	−3	3	0
Asthma exacerbations							
	Annual total		0.29	0.84	0	19	0
	Hospital admission		0.01	0.08	0	1	0
	Primary care management		0.18	0.38	0	1	0

[a] A: including overlapping days; B: excluding overlapping day; C: pass excess days to next interval; D: share excess days proportionally between intervals; E: interval set as 365 days; F: adjusted the beginning and end intervals

fixed effects models with a mix of lagged dependent variables, endogenous and predetermined regressors as well as strictly exogenous regressors. We implemented this estimator using Roodman's xtabond2 algorithm [22] which is an add-on to the STATA software.

Results

Measuring adherence

Overall, 292,738 patients with 1,181,033 patient-years of data were included in this study. Descriptive statistics for each PPR measurement strategy are listed in the top half of Table 1. By design, strategies 2 and 5 had a maximum possible PPR value of 100 %, while for those strategies in which PPR can exceed 100 %, similar extreme ranges were observed. For the base-case (strategy 1), there were 28.2 % of patient-years with PPR that exceeded 100 %, while 32.0 % of patient-years had PPR values lower than 50 %. The proportions of patient-years below 20 % were consistent across all five strategies.

The empirical relative frequency functions of all PPR measurements are depicted in Fig. 2 for each of strategies 1–4.

Since all of the methods had a similar frequency profile for PPR, the strategy considered to be the most clinically appropriate was selected to take forward for modelling purposes. In clinical practice, patients are unlikely to discard remaining doses when they receive a new prescription

Table 2 Data definitions

Patient characteristics	Description
Age in years	The age of the patient in years
Years in study	The number of years since the patient first met the inclusion criteria for the study
SABA use	Indicator of asthma control. Prescribing of over 10 doses per day on average over the year indicates poor control (1 = patient has received prescriptions for over 10 SABA per day)
BTS/SIGN step	Indicator of asthma severity. The treatment step taken from the British Guideline on the Management of Asthma [11]. Patients treated within steps 2–5 are included in the study
Annual change in step	Indicator for whether a patient has increased or decreased in severity from their previous year in the study
Annual total asthma exacerbations	Number of asthma exacerbations in the year
Hospital admission	Asthma exacerbation requiring a hospital admission (1 = the patient has been admitted at least once in the year for asthma exacerbation)
Primary care management	Asthma exacerbation treated within primary care (1 = the patient has been treated within primary care at least once in the year for asthma exacerbation)

or at the end of a year, especially if the new prescription is for the same medicine. It is likely that patients will have gaps in prescribing due to missing data or when newly entering into, or leaving their registration at their general practice. Further, once a patient receives enough medicine to cover every day of the year, they should receive no additional clinical benefit from any additional doses prescribed. These practices are most closely simulated by strategy 5, therefore it was this measure which we used to proxy adherence to ICS and which was subsequently used for modelling purposes.

Modelling adherence

Using PPR measured using strategy 5, three sets of estimation results are presented in Table 3: for all patients (column 1) and gender-specific in columns (2) and (3). The periodicity in the model was annual and as each fitted model contains 2 prior lags of *PPR*, only patients recording data in 3 or more years were included in the estimation runs; patient numbers are reported under *N*. Estimates and associated t-statistics (ratio of estimate to standard error) are reported. Regression controls were allocated into three major categories: patient characteristics, persistence and asthma exacerbations. Baseline values for categorical variables are indicated by zero coefficients, and so results can be interpreted relative to a patient who is at BTS/SIGN treatment step 2 with no high use of SABA in the current year and who has had no exacerbations of either type in the prior year. Note that descriptive statistics associated with the controls were reported earlier in the bottom half of Table 1.

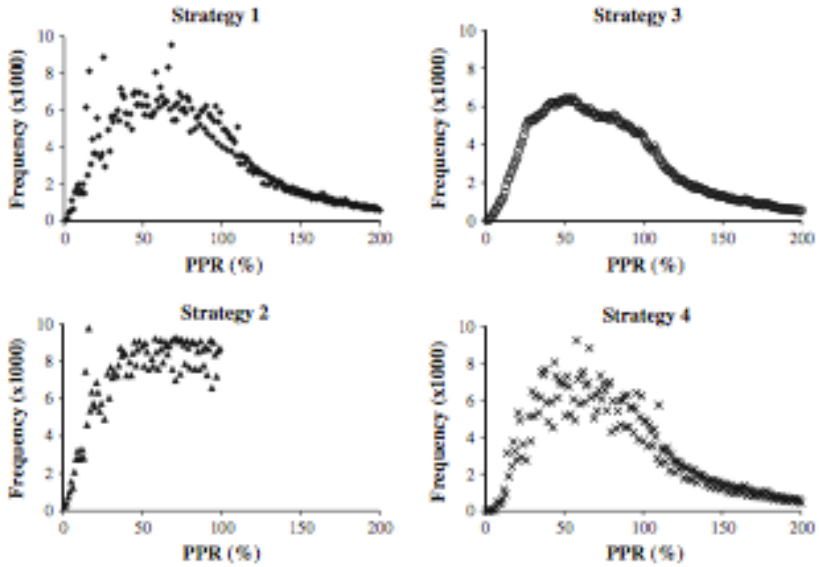


Fig. 2 PPR empirical relative frequency function

Table 3 System GMM estimation results

	(1)		(2)		(3)	
	All		Male		Female	
Patient count *N*	97,456		42,740		54,716	
	Estimate	T-stat	Estimate	T-stat	Estimate	T-stat
Intercept	24.757	65.02	25.725	41.62	23.892	49.85
Patient characteristics						
Age in years	0.110	37.38	0.108	25.24	0.115	28.03
Years in study	0.257	20.56	0.249	12.80	0.264	16.02
SABA use, no = 0	0		0		0	
SABA use, yes = 1	5.108	29.55	4.898	20.58	5.380	21.74
BTS/SIGN step 2	0		0		0	
BTS/SIGN step 3	−1.472	−13.79	−1.578	−9.96	−1.353	−9.42
BTS/SIGN step 4	−2.513	−20.19	−2.551	−14.66	−2.365	−13.91
BTS/SIGN step 5	−4.014	−8.62	−2.126	−2.81	−4.868	−8.28
Annual change in step	2.595	31.37	2.247	17.60	2.799	25.83
Persistence						
PPR_{-1}	0.503	141.89	0.500	88.13	0.507	111.05
PPR_{-2}	0.102	34.82	0.099	21.52	0.103	27.06
Exacerbations						
Total in current year	0.241	1.43	0.655	2.71	−0.090	−0.42
Prior year hospital admission, no = 0	0		0		0	
Prior year hospital admission, yes = 1	1.653	2.04	2.511	2.11	0.735	0.67
Prior year primary care, no = 1	0		0		0	
Prior year primary care, yes = 1	0.942	6.90	1.064	4.71	0.912	5.31
Prior year interaction	−0.378	−0.34	−1.024	−0.58	0.989	0.68

Baseline values for categorical variables are indicated with a zero coefficient: being a patient at BTS/SIGN treatment step 2 with no high use of SABA in the current year and no exacerbations of either type in the prior year

Persistence

The positive, statistically significant estimates of the coefficients of lagged *PPR* (PPR_{-1} is current *PPR* lagged by 1 year, and PPR_{-2} lags it by 2 years) show that the patient's history of adherence behaviour has a strong and reinforcing influence on their current attitude towards ICS adherence.

Characteristics

Adherence increases with patient age (+0.11 %/year; t = 37.4) as too it trends positively the longer the patient remains in contact with the prescriber (years in study: +0.26 %/year; t = 20.6). High SABA use is indicative of poor asthma control over a sustained period, when SABA was used in this manner our estimation results indicated that adherence to ICS was significantly boosted by approximately 5 % alongside it (+5.1 %; t = 29.6). As might be expected adherence worsened as patients were treated at higher steps in the BTS/SIGN guidelines (step 2 is the base); however, it is important to note the modification that should an annual worsening in asthma status occur (i.e. 'annual change in step' = 1 or more), it prompted the patient to reconsider their adherence behaviour and improve it +2.6 % per increment (t = 31.4). The flip side to this was that a patient presenting with an annual improvement in their asthma status (i.e. 'annual change in step' = −1 or lower) was expected to worsen in adherence.

Exacerbations

The positive estimate (+0.241 %/attack; t = 1.43) implied that adherence improved as the number of exacerbations (hospital admit plus managed in primary care; assumed endogenous) increased, although the estimate did not significantly differ from zero. Included into the model and separated by destination of care were indicators of exacerbation occurrence in the previous year; these variables were

predetermined. The evidence was now statistically stronger: patient's behavioural response to the occurrence of past exacerbations was to increase their adherence to ICS, where the +1.653 % estimate (t = 2.04) of the adherence effect was greater than +0.942 % (t = 6.9) than if all prior year exacerbations were managed solely in primary care.

Gender differences

The differences that emerged when stratifying by gender focussed mainly on response to exacerbations. As the total number of current year exacerbations increased males responded by improving their decision to adhere to ICS whereas amongst females this was insignificant (males: +0.655 %/attack; t = 2.71 vs females: −0.09 %/attack; t = −0.42). Also in evidence is the response to prior year hospital-treated exacerbation, where the response by males sees a significant improvement in their current decision to adhere to ICS (+2.511 %; t = 2.11), whereas amongst females their response is insignificant (+0.735 %; t = 0.67).

Discussion

Prescription possession ratio results were not greatly affected by the method chosen, except for the censoring or restricting of measures to a maximum of 100 % in strategies 2 and 5. Larger variances were reported for strategies 1, 3 and 4, caused by outliers but mainly by large numbers of values generated in excess of 100 % (observed to be 28.4 % of patient-years). By censoring these at 100 %, the mean and variance of PPR must decrease. The presence of under-prescribing was also highlighted (observed to be 32.1 % of patient-years in which PPR < 50 %). The clinical reasons for both eventualities, over- and under-prescribing, warrants further investigation. Amongst possible reasons for over-prescribing may be an absence of understanding by the prescriber about what has been prescribed previously, or by patients receiving but not filling prescriptions. Under-prescribing may be caused by the patient's desire to avoid taking the medicine, by the physician or the patient deeming it to be appropriate despite not being in line with treatment guidelines [4].

The modelling results reinforce prior expectations that the better was a patient's health the lesser was the incentive for them to adhere to a long-term ICS regimen. On the other hand, the model showed that when adverse exacerbation events occurred, patients' ICS adherence would, at least on average, be forcibly improved. Moreover, younger age remained a significant factor detrimental to adherence for both sexes; for example, the ICS adherence prediction from the fitted model for a 16 year-old with step 2 disease averages barely more than 25 %. Admittedly, 'high' concomitant use of SABA increased the 16 year-olds' prediction to approximately 30 %, but even so when coupled with evidence of strong behavioural persistence over time the young asthmatic was expected to be non-adherent to ICS for some years, and therefore should arguably be a prime target for adherence-promoting policy interventions.

Strengths and limitations

Other studies have found PPR to be reflective of the medicine possession ratio (MPR) [23]; a measure of adherence frequently used in studies using prescription fill data rather than prescribing data. PPR can be a very useful tool for measuring adherence using the very rich source of retrospective data available in the UK, however, it is difficult to interpret the accuracy of the measure without comparing the adherence measured by PPR against adherence measured directly; but, the precision of the method appears to be good. Therefore, PPR should be used with caution to determine actual levels of adherence, but if used can be very valuable to measure changes or differences in adherence over time.

The use of the CPRD prescribing data to calculate adherence, with its large rich source of clinical and patient characteristic data, allows the impact of other patient and clinical characteristics that may affect adherence to be considered. However, there are several known limitations of using retrospective databases for analysis that would be expected to affect some of the patient records; including missing or incorrectly recorded information and incentives giving rise to record specific types of data and which assign lower priority to others. Despite these limitations, the large data source allows the impact on conclusions of these limitations (as long as they are considered in study design) to be minimal.

There are also many factors that could affect adherence, but cannot be measured in this setting. Examples of these would be patient attitudes to their condition or medicine, or the reasons for the decisions taken by the health care professional to prescribe ICS. The PPR measure uses the assumption that patients should be prescribed a regular daily dose of ICS to treat their asthma; however the intention of the health care professional to prescribe a daily dose is not available. If unobserved heterogeneity is integral to the study outcomes, then it would need to be considered in any modelling of the data and in the inferences drawn. While the use of fixed effects in modelling goes some way towards mitigating the deleterious effect of unobserved heterogeneity, it is still only a partial solution.

Conclusion

An annual measure of asthma patients' adherence to ICS, the PPR, measured using CPRD data, was constructed and

found to be a useful measure for signalling, or measuring adherence changes over time. The chosen PPR methodology simulated clinical use of ICS most closely; including overlapping days, excess days passed to the next interval, considering gaps in the denominator, with censoring at 100 %. The methods for calculating PPR could be applied to other chronic conditions; however the method chosen must be based on knowledge of the specific clinical setting and disease-medicine characteristics.

A patient-level statistical model of ICS adherence was constructed, controlling for a range of individual patient factors. The modelling results identified many characteristics which would indicate which asthma patients and at what points in their treatment cycle they would be at increased risk of low adherence. These risk factors included those with poor adherence in the previous year, younger patients, higher treatment step, and those patients who have not recently experienced an exacerbation.

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Conflicts of interest None.

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