Analysis of treatment of respiratory disease in the United Kingdom and United States

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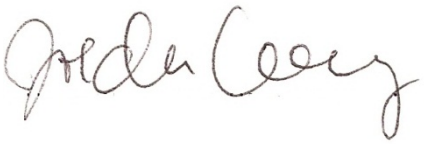

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Glossary:

Acronym	*Meaning*
ACS	American Community Survey
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATS	American Thoracic Society
aPDD	Assumed prescribed daily dose
BDP	Beclometasone dipropionate
BI	Business intelligence
BNF	British National Formulary
BTS	British Thoracic Society
CAT	COPD Assessment Test
CCTS	Center for Clinical and Translational Science
CFC	Chlorofluorocarbon
CHI	Community Health Index
CI	Confidence interval
CMB	Combination therapy
COPD	Chronic obstructive pulmonary disease
CPU	Central processing unit
DDD	Defined daily dose
EHR	Electronic health record
ERS	European Respiratory Society
DDD	Defined daily dose
DPI	Dry powder inhaler
FACET	Formoterol and Corticosteroids Establishing Therapy
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FV	Forth Valley
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GGC	Greater Glasgow & Clyde
GMS	General Medical Services
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
GPASS	General Practice Administration System for Scotland
GROS	General Register Office for Scotland

HD	High dose
HFA	Hydrofluorocarbon
HPA	Hypothalamic-pituitary-adrenal
IBM	International Business Machines Corporation
ICD-9 CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICS	Inhaled corticosteroid
INSPIRE	Investigating New Standards for Prophylaxis in Reducing Exacerbations
IQR	Interquartile range
ISD	Information Services Division
KDD	Knowledge discovery in databases
KY	Kentucky
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LD	Low dose
LES	Locally enhanced service
LTRA	Leukotriene receptor antagonist
mcg	Microgram
MCN	Managed Clinical Network
MD	Medium dose
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mMRC	modified Medical Research Council
MPR	Medication possession ratio
MRC	Medical Research Council
NF	Normal form
NHLBI	National Heart, Lung and Blood Institute
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NRS	National Records of Scotland
NSS	National Services Scotland
OCS	Oral corticosteroid
OR	Odds ratio
PDC	Proportion of days covered
PDD	Prescribed daily dose
PEFR	Peak expiratory flow rate
PIS	Prescribing Information System

pMDI	Pressurised metered dose inhaler
PRISMS	Prescribing Information System for Scotland
QOF	Quality Outcomes Framework
RAM	Random access memory
RCT	Randomised controlled trial
RD	Risk difference
RDMS	Relational database management system
REMS	Risk evaluation and mitigation strategy
RPS	Royal Pharmaceutical Society
RR	Relative risk
SABA	Short-acting beta agonist
SAMA	Short-acting muscarinic antagonist
SD	Standard deviation
SEM	Standard error of the mean
SMART	Salmeterol Multicenter Asthma Research Trial
SMART®	Symbicort® inhaler Maintenance And Reliever Therapy
SMC	Scottish Medicines Consortium
SNS	Scottish Neighbourhood Statistics
SIGN	Scottish Intercollegiate Guideline Network
SIMD	Scottish Index of Multiple Deprivation
SIPBS	Strathclyde Institute of Pharmacy and Biomedical Sciences
SQL	Structured query language
TORCH	Towards a Revolution in COPD Health
TP	Theophylline
TRISTAN	Trial of Inhaled Steroids and Long-Acting $Beta_2$ Agonists
TTD	Time to discontinuation
UK	United Kingdom
UKY	University of Kentucky
USA	United States of America
VA	Veterans Affairs
VPN	Virtual private network

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Abstract:

INTRODUCTION: Asthma and chronic obstructive pulmonary disease (COPD) affect 8% and 5% of the population, respectively, in the United Kingdom (UK) and the United States (USA). A variety of medicines are available but how they are utilised in real practice is not fully understood. The aim of this work was to describe and compare the treatment of asthma and COPD in the UK and USA.

METHODS: Three retrospective databases (two administrative and one electronic health record datasets) were formed from sources in National Health Service (NHS) Scotland, NHS Forth Valley, Scotland, and Kentucky, USA. Several analyses were conducted, including mapping and evaluation of national medicine utilisation, evaluation of adherence/persistence with chronic therapy, classification of therapy against guideline recommendations, and appraisal of inhaled corticosteroid (ICS) prescribing.

RESULTS: National medicine utilisation figures indicated an increasing preference over time for combination therapy with ICS and long-acting beta agonist (LABA) inhalers. Therapy for asthma demonstrated some unanticipated trends, with widespread use of high-dose combination therapy in up to one-third of patients and a lack of standardised therapy approach by clinicians at step 2/3. For COPD, spirometry data was unable to verify diagnosis in up to a quarter of patients, and approximately one-third of patients received unlicensed doses of combination therapy. Adherence and persistence with chronic medicine in both databases was better amongst women, with advancing age and with oral therapy. Direct comparisons between the UK and USA were difficult due to the different healthcare structures and methods for data collection, but doses of ICS in children appeared more aggressive in the USA.

CONCLUSION: The treatment of respiratory disease can be optimised in several clinical areas, most notably with ICS prescribing. Further research and quality improvement measures are needed to improve the care of respiratory disease.

Summary:

INTRODUCTION: Asthma affects approximately 8% of the population in both the United Kingdom (UK) and the United States (USA), and is thought to be expanding on the global front due to growth in urbanisation. Symptoms of breathlessness can be episodic or chronic, and disease severity ranges from mild to a chronic and debilitating form. Chronic obstructive pulmonary disease (COPD) is largely the long-term result of cigarette smoking and has a prevalence of approximately 5% in both countries. Unlike asthma, symptoms are chronic and progressive, and may prove ultimately terminal. Both diseases can be treated with a variety of inhaled medicines, but knowledge on the utilisation of said therapies is often confined to ideal conditions within clinical trials and guidelines; how they are utilised in 'real world' practice is not greatly known, but may have the potential to inform on quality improvement in care. The aim of this work was to describe and compare the treatment of asthma and COPD in the UK and USA.

METHODS: Three retrospective databases were utilised to evaluate various aspects of respiratory disease. The Prescribing Information System (PIS) database was formed from a dataset of pharmacy dispensing data across National Health Service (NHS) Scotland and was utilised to investigate geographic and temporal trends in overall respiratory medicine utilisation in Scotland. Two further regional datasets were obtained from NHS Forth Valley, Scotland (the 'FV database') and Kentucky, USA (the 'KY database'). These databases were formed by electronic health record data and third-party administrative data, respectively, and were utilised to carry out a variety of further analyses, including evaluation of adherence/persistence with chronic therapy, classification of prescribed therapy against prevailing guideline recommendations, and appraisal of inhaled corticosteroid (ICS) prescribing.

RESULTS: Geographic mapping of medicine utilisation from the PIS database suggested a concentrated prevalence of COPD within the central belt of Scotland, whereas asthma prevalence appeared more sporadic. Several different metrics quantifying 10-year national utilisation trends for pharmacy dispensing indicated increasing prescribing preference for combination therapy with ICS and long-acting beta agonist (LABA) inhalers. Evaluation of medicine utilisation in NHS Forth Valley compared to the whole of Scotland suggested it to be an adequate and representative sample. For asthma, mean doses for ICS in both the FV and KY

databases were higher than anticipated, although this was particularly the case for children in KY. Adherence to chronic therapy was low, with 55.3% of medicine use in the FV database and 72.8% of medicine use in the KY database classified as an undersupply. Persistence mirrored these trends, with demonstration in the KY database of a large drop-off after the first issued prescription. Patients with asthma receiving their first combination therapy inhaler were shown to have rapid and unanticipated ICS dose escalation in the FV database, but a general lack of previous ICS therapy in the KY database. For COPD, available spirometry data in the FV database indicated 24.8% of patients failed to meet diagnostic criteria for COPD despite being listed on the practice diagnostic register and being actively treated for the disease. Adherence was higher among patients with COPD (compared to those with asthma), with rates of undersupply at 42.0% and 59.2% in the FV and KY databases, respectively. Persistence rates held with similar trends in asthma, with higher rates among patients who were male, of increasing age and taking oral therapy (theophylline). An evaluation of prescriptions for combination therapy revealed under-dosing rates ranging from 14.1 to 31.3% in the FV database, and 8.3 to 14.0% in the KY database, depending on the specific inhaler. Lastly, an evaluation of spirometric testing in the FV database revealed a high rate (91.3% overall) of utilisation, but suggested testing to be less likely performed in women and for regular monitoring of disease progression.

CONCLUSION: Several goals were achieved through this research, including (1) pinpointing clinical areas for continuing quality improvement, such as appropriate dosing of ICS in asthma and COPD, (2) evaluation of several metrics and methods for medicine utilisation to inform future research, and (3) creation of recommendations to improve the usefulness of future clinical database work worldwide.

Chapter 1:

Background

1.1 Definition

Chronic respiratory disease affects hundreds of millions of people worldwide across all ages and from all nationalities and socioeconomic backgrounds. Despite their widespread nature, diseases such as asthma and chronic obstructive pulmonary disease (COPD) remain largely unaddressed and poorly prevented (World Health Organization, 2007). Unless fully recognised they will remain a leading cause of morbidity and mortality across the globe.

Asthma is defined as "*a chronic inflammatory disorder of the airways... associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing... but variable... often reversible either spontaneously or with treatment*" (Global Initiative for Asthma, 2012). COPD is a "*preventable and treatable lung disease… characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response… exacerbations and comorbidities contribute to the overall severity*" (Global Initiative for Chronic Obstructive Lung Disease, 2013). The definition of COPD has changed over time to reflect both the clinical components of the disease (chronic bronchitis) and the characteristic anatomical changes (emphysema) (World Health Organization, 2007).

Asthma and COPD differ in several important physiological and clinical respects. Inflammation plays a large role in both diseases but through different mechanisms. Early characterisations of asthma were based primarily on allergy-induced bronchospasm in small airways (Chu *et al.*, 2005); this has since evolved to recognise the contribution of inflammation mediated by eosinophils and CD-4^+ lymphocyte infiltration in the airways (Fabbri *et al.*, 2003). COPD, however, is thought to be mediated by macrophage and CD-8^+ lymphocyte recruitment, which cause long-standing mucus hyper-secretion and destruction of lung parenchyma (Barnes *et al.*, 2003; Stockley *et al.*, 2009). The airway hyper-responsiveness in asthma is episodic, largely reversible and responsive to corticosteroids (Gibson *et al.*, 2009), unlike that of COPD, which is chronic, progressive and debilitating. Causation is another important difference between asthma and COPD. Cigarette smoke is the primary risk factor in the development of COPD, resulting from chronic inflammatory changes induced by the direct inhalation of noxious agents. Smoking

contributes to up to 73% of COPD mortality (Mannino *et al.*, 2007), with the individual risk of mortality in a patient positively correlating with amount of tobacco used (Doll *et al.*, 2004). However, occupational exposure to other dusts/fumes and environmental exposure to biomass fuels also contribute to the development of COPD. The pathogenesis of asthma is less clear and has been associated with a variety of influences, including exposure to allergens, the presence of atopy and genetic predisposition. Other contributors, such as the 'hygiene hypothesis', have also been widely debated over the past 20 years (Strachan, 1989; Strachan, 2000). Tobacco smoke, while a significant contributor to the frequency of exacerbations of asthma, lacks the direct causative role in the development of the condition that it has in COPD.

Despite these differences, some patients have characteristics of both diseases, as patients with long-standing asthma may develop progressive decline in their lung function over time (Lange *et al.*, 1998), largely a function of airway remodelling induced by poorly controlled disease and chronic inflammation (Tashkin *et al.*, 2003). One estimate found that 19% and 17% of patients in the United Kingdom (UK) and United States (USA), respectively reported the concurrent presence of asthma and COPD (Soriano *et al.*, 2003). Sometimes termed the 'overlap syndrome', patients with both asthma and COPD experience more exacerbations and a poorer quality of life compared to patients with COPD alone (Hardin *et al.*, 2011). Patients with concurrent asthma and COPD are often excluded from large-scale clinical trials due to the confounding effect of one disease on the other.

1.2 Prevalence

An estimated 5.2 million people in the UK, or approximately 8% of the population, currently are estimated to have asthma and approximately one fifth of these are children (Asthma UK, 2008). Overall prevalence, particularly in children, has increased over the last five decades although there is some suggestion it has plateaued since the 1990s (Anderson *et al.*, 2007). Five percent of all patients in Scotland consulted their general practitioner (GP) for the care of asthma during fiscal year 2011/12 (Practice Team Initiative, 2013a). In the USA, 25 million people are estimated to have asthma, with nearly one quarter of them children (Akinbami *et*

al., 2012). Overall prevalence has increased steadily from 7.3% in 2001 to 8.4% in 2010 (Akinbami *et al.*, 2012).

Asthma is most common among school-aged children and accordingly this age group is the most widely studied. The incidence of asthma is highest among boys before puberty, switching over to be greater in women for the remainder of adolescence and persisting throughout adulthood (de Marco *et al.*, 2000). Despite a smaller number of cases, asthma in the elderly is particularly pertinent as this group experiences the highest rate of disease-related mortality, accounting for 50% of asthma related deaths (Stupka *et al.*, 2009).

The prevalence of asthma in countries such as the UK and the USA is among the highest in the world, with over three-fold the rates in Russia and China (Masoli, Fabian*, et al.*, 2004). Asthma symptoms have seen an increase over time particularly in developed countries, which are thought to be the result of urbanisation and the impact of living in population-dense areas. An analysis of neighbourhood areas with elevated rates of childhood asthma hospitalisations in New York City found correlations with lower household incomes, higher percentages of minority residents, poorer quality housing, and increased exposure to environmental pollutants (Corburn *et al.*, 2006). As the world becomes more 'westernised', the prevalence of asthma is expected to rise.

There are an estimated 3.7 million people with COPD in the UK, although fewer than 1 million are thought to be aware of their diagnosis (British Lung Foundation, 2007). In Scotland, 1.9% of all patients consulted their GPs for COPD in fiscal year 2011/12 (Practice Team Initiative, 2013b). The American Lung Association estimated that over 12 million people in the USA had COPD in 2006, with up to 24 million with some evidence of impaired lung function (American Lung Association, 2008). The prevalence of COPD has remained relatively stable at 5.1 to 5.7% from 1998 to 2009, although geographic differences in the USA are evident, with a prevalence rate of 7.5% in the East South Central region, encompassing Kentucky, Tennessee, Mississippi and Alabama, compared to 3.9% in the Pacific region of Washington, Oregon, and California (Akinbami *et al.*, 2011).

As the destructive changes in lung tissue from smoking are a longitudinal process, COPD commonly presents after 35 years of age, unless mediated by rarer genetic causes such as alpha-1-antitrypsin deficiency. Peak prevalence occurs in the mid-70s for both sexes, favouring men over women across the age spectrum (van Durme *et al.*, 2009). Recently, an increasing burden of COPD in young women has been noted in several analyses, both in terms of diagnosis and mortality (Centers for Disease Control and Prevention, 2008; Soriano *et al.*, 2000; van Durme *et al.*, 2009), which may be the result of the historical time-lag in the uptake of tobacco smoking between men and women (Lopez *et al.*, 1994).

Prevalence estimates discussed are point-prevalence estimates from cross-sectional population surveys unless otherwise noted. However, comparisons in prevalence estimates for asthma and COPD must be interpreted cautiously, as they are known to vary dramatically according to diagnostic criteria, guideline classification, heterogeneity in population assessed, and patient understanding and/or awareness of disease (Buist *et al.*, 2007; Halbert *et al.*, 2006; Lindberg *et al.*, 2005; Nathell *et al.*, 2007; Shahab *et al.*, 2006). Patient self-reporting of disease generally yields the highest overall estimates of disease burden, while confirmatory physiological documentation of airflow limitation by lung function testing is the most restrictive definition (Lange *et al.*, 1989).

1.3 Clinical guidelines

The treatment of asthma and COPD is driven by clinical guidelines from several national and international groups. Guidance on the treatment of asthma is available from the British Thoracic Society and the Scottish International Guideline Network (BTS/SIGN) collaboration in the UK, the National Heart, Lung, and Blood Institute (NHLBI; a division of the National Institutes of Health [NIH]) in the USA, and the Global Initiative for Asthma (GINA) worldwide. Guidance for COPD is produced by the National Institute for Health and Clinical Excellence (NICE) in the UK, the American Thoracic Society (ATS) in the USA and the European Respiratory Society (ERS) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in Europe and worldwide, respectively. The discussion of treatment in this text focuses on the latest guidance from BTS/SIGN (for asthma) and NICE (for COPD), with differences to other guidelines and key temporal updates noted where appropriate.

1.3.1 Asthma

The BTS/SIGN 2012 guideline recommends that a diagnosis of asthma should be considered in any patient with recurrent respiratory symptoms such as wheezing, cough, difficulty breathing or chest tightness (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2012). A personal history of atopic disease, a family history of asthma/atopy and exposure to allergens also contribute to clinical suspicion. Demonstration of varying airflow limitation over time by forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR) measurement further supports a diagnosis. Due to this variability, airflow limitation is not specific to an asthma diagnosis nor is a normal result able to exclude the diagnosis. Accordingly, some patients may either be diagnosed clinically through 'watchful waiting' or with a trial of treatment and resultant improvement in symptoms. The control of asthma is based on assessment of several factors (Table 1.1) with the ultimate treatment aim being total control of disease with no symptoms present. As this may not be possible in every patient, the aggressiveness of treatment is driven by the preferences of the patient and prescriber with regard to the right balance between disease control and potential side effects or inconvenience of therapy.

Table 1.1: Considerations when assessing asthma control

Factors
Presence of daytime symptoms
Presence of night-time awakenings
Need for rescue medication
Exacerbations
Limitation in activity (e.g. exercise)
Lung function (FEV_1 or PEFR)
Minimal adverse effects from medication

Treatment recommendations are provided through step-wise algorithms for adults and adolescents greater than 12 years old, children 5 to 12 years old and children under 5 years old. For adults and adolescents, initial treatment starts with a short-acting beta agonist (SABA) on an 'as needed' basis for control of intermittent symptoms (Figure 1.1). Patients with more persistent symptoms should have regular preventer therapy introduced, preferably with an inhaled corticosteroid (ICS). For

patients with inadequate control at this stage, the addition of a long-acting beta agonist (LABA) is recommended at step 3, although the dose of ICS at which this should occur is not specific and is in the range of 200 to 800 micrograms beclometasone dipropionate (BDP) chlorofluorocarbon (CFC) equivalent daily. Further escalation of therapy involves an increase in the ICS dose up to 2,000 micrograms BDP-equivalent daily, the addition of other adjunctive therapies such as leukotriene receptor antagonists (LTRA), theophyllines (TP) or beta-agonist tablets and finally, the addition of maintenance oral corticosteroids (OCS) for severe, refractory disease. For children 5 to 12 years old, the same algorithm is utilised with half the dose of ICS recommended at each step.

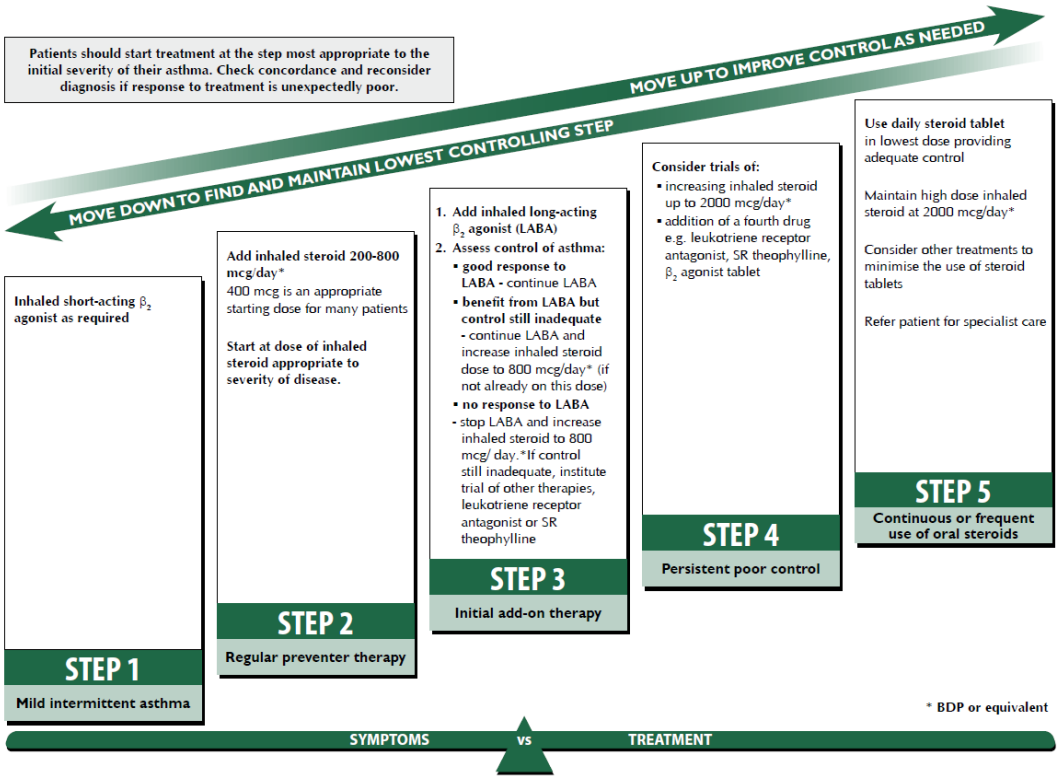


Figure 1.1: Stepwise management of adult and adolescent asthma in BTS/SIGN 2012
Reprinted with permission from (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2012)

Prescribing guidance from both GINA and NHLBI also utilise step-wise approaches for the treatment of asthma; however, there are some key differences in recommendations at step 3 (Table 1.2). For adults and adolescents, GINA gives a clear preference for low-dose combination therapy (CMB) at 200 to 500 micrograms BDP-equivalent daily (Global Initiative for Asthma, 2012). NHLBI, on the other hand,

gives equal weight to either low-dose combination therapy (200 to 500 micrograms BDP-equivalent daily) or medium-dose ICS alone (500 to 1,000 micrograms BDP-equivalent daily) (National Heart Lung and Blood Institute, 2007). For children 5 to 12 years old, GINA recommends medium-dose ICS alone at a dose of 200 to 400 micrograms BDP-equivalent daily over combination therapy, while NHLBI maintains an equal recommendation between low-dose combination therapy (100 to 200 micrograms BDP-equivalent daily) and medium-dose ICS alone (200 to 400 micrograms BDP-equivalent daily).

Table 1.2: Step 3 prescribing guidance for adults and adolescents
** differences in dose ranges exist between guidelines*
LD = low-dose; MD = medium-dose; HD = high dose

Guideline *	First choice	Alternatives
BTS/SIGN	LD- or MD-ICS plus LABA	MD-ICS alone LD-ICS plus LTRA, TP or beta-agonist tablet
GINA	LD-ICS plus LABA	MD- or HD-ICS alone LD-ICS plus LTRA or TP
NHLBI	LD-ICS plus LABA MD-ICS alone	LD-ICS plus LTRA or TP

In versions of the BTS guideline during the 1990s asthma step therapy focused primarily on increasing doses of ICS in step 3 and 4, as LABAs were only recently licensed and their relative benefits in combination therapy had not been extensively studied (British Thoracic Society, 1997; British Thoracic Society et al., 1990; British Thoracic Society et al., 1993). Since 2003, the recommendation for combination therapy has persisted in both guidelines (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2003; Global Initiative for Asthma, 2002).

All guidelines agree that after achieving good control of asthma symptoms for at least three months, step-down of therapy should be considered, with a reduction in ICS dose of 25 to 50% every three months thereafter, with the understanding that symptoms may worsen and therapy may have to be re-initiated at the higher dose.

1.3.2 COPD

Current recommendations from NICE state that a diagnosis of COPD should be considered in any patient over 35 years of age with symptoms of dyspnoea, chronic cough or sputum production, frequent wheeze/bronchitis and exposure to risk factors including a smoking history of 20 pack years (National Institute for Health and Clinical Excellence, 2010). The diagnosis should be confirmed by spirometry, with a post-bronchodilator FEV_1 to forced vital capacity (FVC) fixed ratio of less than 0.7 as the threshold for airflow obstruction. From this, the severity of airflow limitation can be subcategorised into four stages (Table 1.3).

Table 1.3: Classification of airflow limitation severity in COPD

Stage	**FEV_1 percent**
1 (mild)	≥ 80% predicted
2 (moderate)	50-79% predicted
3 (severe)	30-49% predicted
4 (very severe)	< 30% predicted, or < 50% predicted with respiratory failure

Guidance from NICE, produced in 2004, did not consider patients classified with mild airflow limitation (FEV_1 % predicted of 80% and higher) as having a diagnosis of COPD (National Institute for Health and Clinical Excellence, 2004). This was revised in 2010 to align with the GOLD classification, albeit with the emphasis that symptoms must be present at this stage to support a diagnosis based on evidence that symptoms predict future disease severity and respiratory decline (Bridevaux *et al.*, 2008; National Institute for Health and Clinical Excellence, 2010).

NICE utilises spirometric testing as the primary determinant of a patient's disease severity and initial pharmacological treatment. However, in 2011, GOLD released a new paradigm for classification of disease severity, which includes assessment of a patient's symptom burden using the modified Medical Research Council (mMRC) questionnaire or the COPD Assessment Test (CAT), and the risk of exacerbations, in addition to airflow limitation measured by spirometry (Global Initiative for Chronic Obstructive Lung Disease, 2011) (Figure 1.2). The mMRC questionnaire is a scaled

assessment (classified 0 to 4) of the degree of breathlessness the patient experiences, while the CAT is a measure (scored 0 to 40) of the broader impact of COPD on a patient's life, including symptoms, activity and energy levels (Bestall *et al.*, 1999; Jones *et al.*, 2009). The risk of exacerbations can be determined by two methods: either by an assessment of the patient's number of exacerbations in the previous year, or through the patient's classification of airflow limitation (stage 1 to 4), with the highest risk category taking precedence.

NICE supports the use of the original Medical Research Council (MRC) dyspnoea scale for grading of breathlessness at diagnosis, which utilises a similar scaled assessment, albeit alternatively scored from 1 to 5 (Fletcher *et al.*, 1959). However, this tool has yet to be formally incorporated into a severity algorithm to help determine initial treatment as with the GOLD guideline.

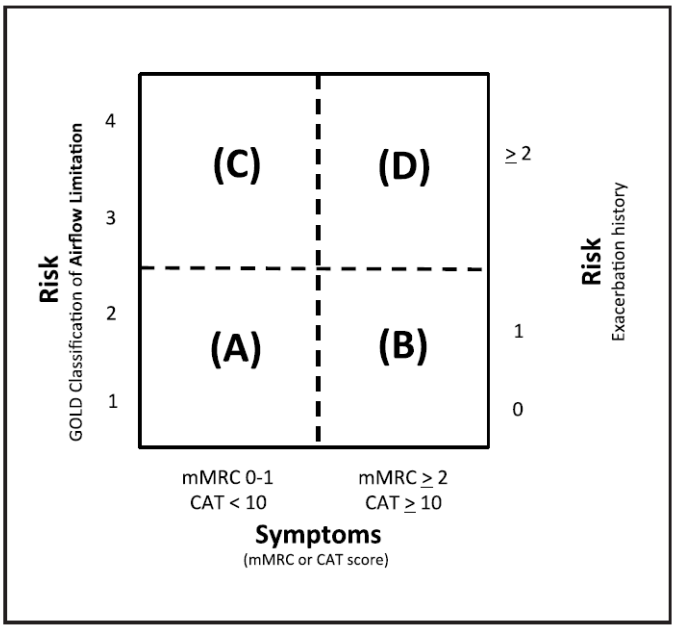


Figure 1.2: Classification of overall COPD severity using combined assessment
Reprinted with permission from (Global Initiative for Chronic Obstructive Lung Disease, 2013)

No pharmacological therapy has been proven to alter the progressive decline of pulmonary function in COPD. Accordingly, the goals of treatment are aimed at reducing symptoms and exacerbations, and improving health-related quality of life. GOLD provides guidance tailored to the results of the combined assessment. Patients with infrequent symptoms and a low risk of exacerbations (Group A) should

be treated with a SABA or short-acting muscarinic antagonist (SAMA) for occasional symptoms. For patients with more frequent symptoms but a low risk of exacerbations (Group B), therapy with long acting bronchodilators (LABA or long-acting muscarinic antagonist [LAMA]) is preferred. However, for patients with a greater risk of exacerbations (Group C), therapy with an ICS in combination with a LABA or LAMA is recommended. For patients with the most severe disease including both a high symptom burden and high risk of exacerbations (Group D), triple therapy with an ICS/LABA and LAMA is recommended.

Similarly, NICE guidance recommends a SABA or SAMA should be offered on an as needed basis for initial treatment, with maintenance inhaled therapy used for patients who remain breathless or have exacerbations despite this treatment (National Institute for Health and Clinical Excellence, 2010). Recommended initial therapies for maintenance include either a LABA or LAMA for patients with an FEV_1 greater than or equal to 50% predicted, or an ICS/LABA or LAMA alone for patients with an FEV_1 of less than 50% predicted. If initial treatment fails to maintain of achieve good control, then further combinations of therapy, including triple therapy with an ICS/LABA and LAMA, may be utilised. The place in treatment for other therapies, such as theophylline or OCS, is reserved for special circumstances, such as in patients unable to use inhaled therapy or patients with severe and advanced disease, respectively. Treatment recommendations from GOLD prior to 2011 were based solely on the degree of airflow limitation and similar to what is currently recommended by NICE (Figure 1.3) (Global Initiative for Chronic Obstructive Lung Disease, 2010).

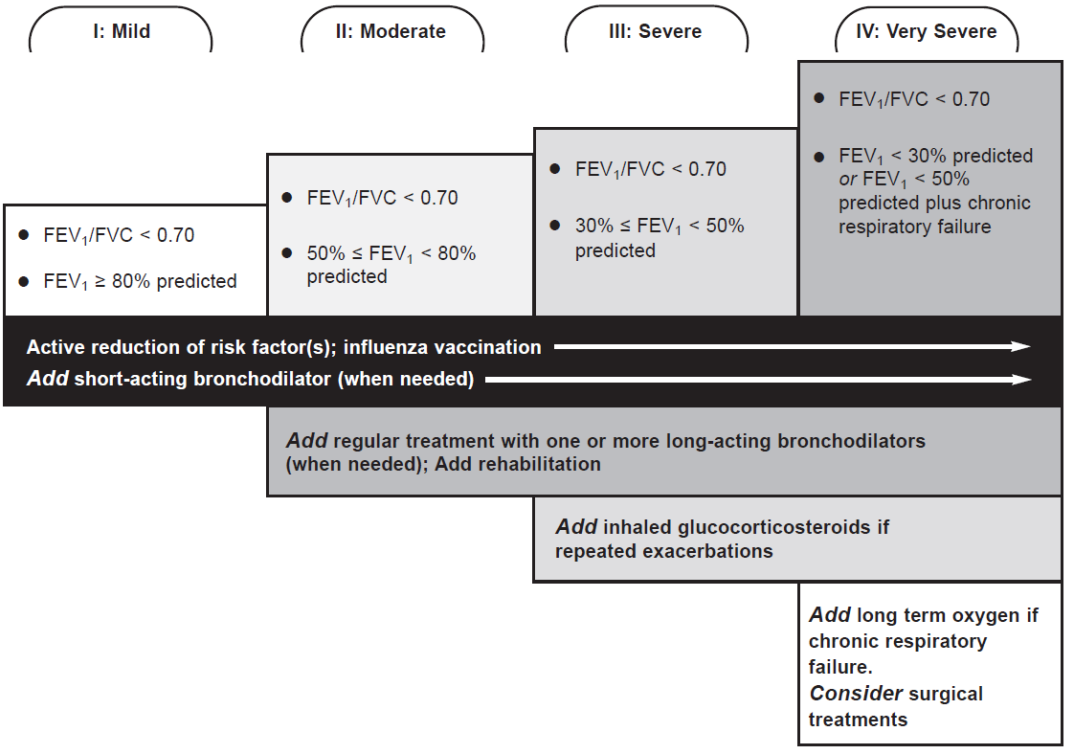


Figure 1.3: GOLD recommended continued treatment for COPD
Reprinted with permission from (Global Initiative for Chronic Obstructive Lung Disease, 2010)

1.4 Comparing respiratory medicines in the UK and USA

The differences between the formulation, availability and dosing of medicines in the UK and USA are important in any international discussion of respiratory disease.

The first factor to consider is how the dose of the inhaler is expressed. Doses of inhaled medicines can be represented in two ways: as the metered dose (ex-valve), or the delivered dose (ex-actuator). The metered dose represents the dose of medicine the inhaler is designed to dispense with a single actuation. However, as some of the dispensed medicine is deposited inside the inhaler prior to exiting the mouthpiece, the dose of medicine available to the patient for inhalation is reduced, thus becoming the delivered dose. Both of these doses are required to be specified by manufacturers in the detailed product information, although the dose under which the product is marketed and commonly prescribed lacks a standardised application and can vary between the UK and USA (Table 1.4).

Table 1.4: Variability in expressed ICS doses in the UK and USA

Medicine	Ex-valve dose	Ex-actuator dose
BDP-CFC (no longer available)	50 or 100 mcg (Becotide®, UK)	42 or 84 mcg (Vanceril®, USA)
BDP-HFA	50 or 100 mcg (Qvar®; UK)	40 or 80 mcg (Qvar®; USA)
Fluticasone (MDI)	50, 125, or 250 mcg (Flixotide Evohaler®, UK)	44, 110 or 220 mcg (Flovent HFA®, USA)
Fluticasone (DPI)	50, 125, or 250 mcg (Flixotide Accuhaler®, UK) 50, 125, or 250 mcg (Flovent Diskus®, USA)	N/A
Mometasone (DPI)	220 mcg (Asmanex Twisthaler®, USA)	200 mcg (Asmanex Twisthaler®, UK)
Fluticasone/salmeterol (MDI)	50/25, 125/25, or 250/25 mcg (Seretide Evohaler®, UK)	45/21, 115/21 or 230/21 mcg (Advair HFA®, USA)
Fluticasone/salmeterol (DPI)	100/50, 250/50, or 500/50 mcg (Seretide Accuhaler®, UK) 100/50, 250/50, or 500/50 mcg (Advair Diskus®, USA)	N/A

The formulation of the inhaled medication must also be taken into account. Inhaled medicines are available as either pressurised metered dose inhalers (pMDI) or dry powder inhalers (DPI). pMDIs dissolve or suspend the active ingredient in an inert aerosolised propellant and generally require coordination of device actuation and inspiratory breath to successfully deliver the medicine into the respiratory tract. DPIs formulate the active ingredient as a fine powder which is inhaled through the action of a sharp inspiratory breath; no propellant is needed because there is no aerosolisation, although lactose may be added as a bulking agent to aid insufflation. The relative effectiveness of either formulation in drug delivery to the lung is highly dependent on patient effort and ability (Geller, 2005), however, the differences in formulation also affect the doses delivered. For instance, Symbicort® is currently available in the UK as a DPI, known as a Turbohaler®, and is available in three ex-valve strengths (100/6 micrograms, 200/6 micrograms and 400/12 micrograms per dose) with a corresponding delivered dose of 80/4.5 micrograms for each metered dose of 100/6 micrograms (Electronic Medicines Compendium, 2014b; Electronic Medicines Compendium, 2014c; Electronic Medicines Compendium, 2014d).

However, in the USA, Symbicort® is available as a pMDI, available in two ex-actuator strengths, 80/4.5 micrograms and 160/4.5 micrograms per dose, but with a corresponding metered dose of 91/5.1 micrograms for each delivered dose of 80/4.5 micrograms (AstraZeneca, 2012).

Even among pMDIs of the same active medicinal product, attention should be paid to differences in propellant and particle size. Originally, inhalers were formulated using CFC-containing propellants; however in 1987, the signing of the *Montreal Protocol on Substances that Deplete the Ozone Layer* marked the phase-out of CFC-containing products across a number of industries (Montreal Protocol, 1987). This led to the development and use of hydrofluoroalkanes (HFA) as a substitute propellant. With this change in propellant, the size of aerosolised particles was reduced, and the resultant lung deposition increased from less than 20 to over 50% (Berger, 2009). Although smaller particles hypothetically improve efficacy by better penetration into small airways, this effect has not yet been verified clinically.

Lastly, the dose relationship of the medicines being compared is important. There are several ICSs available for the treatment of asthma and COPD and as glucocorticoids, their relative potency can be determined in-vivo by measuring binding affinities and half-lives at the glucocorticoid receptor. However, this measure alone fails to address differences in clinical efficacy noted in trials, due to differences in drug formulation and delivery (Kelly, 2009). Comparative clinical trials provide measures of clinical potency among available products but often use endpoints that are relatively insensitive to change, such as the presence of symptoms, the incidence of exacerbations and changes in lung function (Kelly, 2009). With these considerations in mind, each of the major asthma guidelines have developed guidance on equipotent dose categories for available ICSs, based on the best available amalgamated evidence from manufacturer and laboratory data. BTS/SIGN uses BDP as a reference and suggests equivalent doses of other ICSs, without specific delineation as to what doses are considered low, medium or high (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2012). However, the implied daily ranges (and those used for the remainder of the present text) define 0 to 400 micrograms as low-dose, greater than 400 to 800 micrograms as medium-dose, and greater than 800 micrograms as high-dose. BDP and budesonide are considered equipotent, while fluticasone, mometasone, ciclesonide

and special formulations of BDP (Qvar® and Fostair®) are approximately twice as potent and are prescribed at half the dose. GINA and NHLBI both define ranges for each dose category and for each patient group (adults or children) (Table 1.5).

Table 1.5: Equipotent ICS doses for adults in GINA asthma guideline

Medicine	Low-dose (mcg/day)	Medium-dose (mcg/day)	High-dose (mcg/day)
BDP-CFC	200-500	> 500-1,000	> 1,000-2,000
BDP-HFA	100-250	> 250-500	> 500-1,000
Budesonide	200-400	> 400-800	> 800-1,600
Ciclesonide	80-160	> 160-320	> 320-1,280
Flunisolide	500-1,000	> 1,000-2,000	> 2,000
Fluticasone	100-250	> 250-500	> 500-1,000
Mometasone	200	≥ 400	≥ 800
Triamcinolone	400-1,000	> 1,000-2,000	> 2,000

1.5 Adherence to prescribed therapy

Defined as "*the extent to which a person's behaviour taking medication… corresponds with agreed recommendations from a healthcare provider*," adherence is an important consideration in the study of any disease treatment (World Health Organization, 2003). The use of the associated term 'compliance' has fallen out of favour due to its implication that the patient's duty is to submit to medical advice, rather than work together with healthcare professionals to reach a mutually beneficial agreement for treatment. The term 'concordance' is also used in the UK, which is by some sources synonymous with adherence, and by other accounts refers to the agreed interaction between the patient and clinician, rather than the resulting medication-taking behaviour of the patient (Bell *et al.*, 2007).

Medication non-adherence can be intentional or accidental and can occur at multiple instances within the treatment paradigm. Primary non-adherence refers to when a patient fails to pick up a medication that has been prescribed, while secondary non-adherence refers to behaviours occurring after this point, including taking too much or too little medication, taking it on the wrong dosing schedule, or failing to continue

to take the medication over time, often referred to as non-persistence (Vermeire *et al.*, 2001). Specifically for respiratory disease, poor inhaler technique is also a contributor to secondary non-adherence (Roy *et al.*, 2011). Accordingly, studies should be considered keeping in mind what behaviours can be measured and what aspect of adherence is captured.

Reported adherence rates in respiratory disease are variable depending on the analysis, but average approximately 50%. Increases in the number of doses a day and the number of medications the patient has to take (poly-pharmacy) both negatively affect adherence (Agh *et al.*, 2011; Toy *et al.*, 2011). There also is a correlation between non-adherence and medication cost. An early analysis of primary non-adherence in Scotland before prescription charges were abolished found that 33.1% of patients who failed to pick up their prescriptions paid prescription charges, compared to 17.4% of patients who received their prescriptions at no cost (Beardon *et al.*, 1993).

Poor adherence with treatment is inherently linked to poor disease outcomes. In both asthma and COPD, lower rates of adherence have been associated with more frequent symptoms, poorer lung function on spirometry, lower quality of life and higher rates of hospitalisations (Gamble *et al.*, 2009; Jentzsch *et al.*, 2012; Simoni-Wastila *et al.*, 2012). In COPD, poor adherence to prescribed therapy in the TORCH study resulted in a higher rate of all-cause mortality (26.4 vs. 11.3%, $p<0.0001$) even when adjusted for other prognostic factors (Simoni-Wastila *et al.*, 2012).

1.6 Contemporary topics in respiratory disease

1.6.1 Safety of long-acting beta-agonists in asthma

Shortly after the introduction of LABAs to the market in the UK in 1990, the Serevent® Nationwide Surveillance study evaluated the safety of salmeterol compared to regularly scheduled (opposed to 'as needed') salbutamol for the treatment of asthma. It found a 3-fold increase in mortality for patients prescribed salmeterol, although it failed to reach statistical significance (0.07 vs. 0.02%, $p=0.105$) (Castle *et al.*, 1993). With the subsequent launch of salmeterol in the USA in 1994, the Food and Drug Administration (FDA) required a follow-up post-marketing safety study. The Salmeterol Multicenter Asthma Research Trial

(SMART) study was started and discontinued prematurely in 2003 after an interim analysis confirmed an increase in asthma-related deaths for patients prescribed salmeterol (0.10 vs. 0.02%, relative risk [RR] 4.37, 95% confidence interval [CI] 1.25-15.34) (Nelson *et al.*, 2006).

Using data gathered from all the companies marketing LABA products, the FDA commissioned a large meta-analysis involving 110 studies (Levenson, 2008). Patients receiving LABAs were found to have a higher risk difference (RD) for the composite endpoint (hospitalisation, intubation or death) compared to patients receiving non-LABA regimens (RD 3.63, 95% CI: 1.51-5.75). However, this difference was non-significant for patients receiving LABAs in combination with ICS (RD 0.25, 95% CI: -1.69-2.18). Among over 60,000 patients included in the meta-analysis, only 20 asthma-related deaths occurred. The FDA pursued several actions, including the implementation of a risk evaluation and mitigation strategy (REMS) programme, and changes to product labelling (Food and Drug Administration, 2013b).

Similar action was taken by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, including several informational updates to clinicians (Medicines and Healthcare products Regulatory Agency, 2003; Medicines and Healthcare products Regulatory Agency, 2005; Medicines and Healthcare products Regulatory Agency, 2008; Medicines and Healthcare products Regulatory Agency, 2010). Current advice states that LABAs for the management of chronic asthma should only be used in stable, not acutely deteriorating, patients who fail to gain control on ICS alone and should be withdrawn if no benefit is seen or if therapy step-down is deemed clinically appropriate.

Based on the recommendations made by the FDA, a recent meta-analysis assessed the effects of LABA step-down as compared to maintaining ICS/LABA therapy in patients with good control (Brozek *et al.*, 2012). There were no differences between groups in terms of emergency visits or need for OCS, however, patients who were stepped off LABA treatment had greater reductions in quality of life, fewer symptom-free days and a higher risk of treatment withdrawal due to lack of treatment efficacy (RR: 3.27, 95% CI: 2.16-4.96). As such, the actions by the FDA have received significant criticism (Chan *et al.*, 2012).

1.6.2 Step 3 therapy in asthma

ICS are the most effective medicines available for the treatment of asthma, largely due to their ability to inhibit a variety of cytokines and immune mediators involved in the inflammatory cascade, thereby lessening bronchial hyper-responsiveness (Barnes, 1998). Historically, step therapy favoured the use of ICS dose escalation for patients with poorly controlled asthma. This was based on the assumption that higher doses would correlate with higher suppression of small airway inflammation, despite evidence supporting a dose response curve being limited. Those studies finding a dose-response relationship now indicate the curve is shallow, with most benefit seen at low to medium doses of ICS (Adams *et al.*, 2006). Furthermore, this response is only seen for isolated aspects of asthma control, such as lung function, with little to no effect on symptoms or rate of exacerbations (Adams *et al.*, 2001; Adams *et al.*, 2008). One notable exception is in smokers, who may require larger doses of ICS to achieve the same level of efficacy as non-smokers; although this has been clinically demonstrated, the mechanism remains unknown (Chalmers *et al.*, 2002).

However, the relationship between the dose of ICS and the incidence of adverse effects is well documented. Early studies assessing the effect of ICS on plasma cortisol levels suggested a consistent dose correlation (Clark *et al.*, 1996; Donnelly *et al.*, 1997). A subsequent clinical case series of 33 patients, primarily children, with adrenal crisis related to the use of ICS emerged, causing serious reconsideration of the safety of high doses of ICS, particularly as most of the doses involved were within the recommendations made by BTS and GINA at the time (Todd *et al.*, 2002). Subsequent association with other adverse effects such as linear growth rate suppression, reductions in bone density and cataracts have also motivated the push toward using lower doses of ICS (Lipworth, 1999).

LABAs have been available in the UK and USA since the early 1990s, although their place in asthma therapy has varied. Greening *et al*. (1994) published one of the first randomised controlled trials (RCT) comparing the use of low-dose combination therapy with an ICS and LABA (400 micrograms BDP and 100 micrograms salmeterol daily) against an increased dose of ICS (1,000 micrograms BDP daily) for patients with mild to moderate asthma not controlled on a low-dose ICS alone.

Patients receiving combination therapy were found to have larger increases in mean PEFR, less use of reliever inhalers and fewer daytime and night-time symptoms (Greening *et al.*, 1994). A similar RCT published two years later confirmed the benefits of LABA therapy for patients with more severe asthma on a slightly higher baseline ICS dose (Woolcock *et al.*, 1996). These studies were followed by two meta-analyses and a Cochrane review, all of which confirmed the benefits of low-dose ICS in combination with a LABA for improved lung function, better symptom control and reduced rates of exacerbations as compared to increased doses of ICS (Ducharme *et al.*, 2010; Masoli *et al.*, 2005; Shrewsbury *et al.*, 2000).

Conflicting evidence does exist. The Formoterol and Corticosteroids Establishing Therapy (FACET) group analysed the rate of exacerbations between patients receiving two doses of ICS (200 micrograms or 800 micrograms budesonide daily) with or without a LABA (24 micrograms formoterol daily). Combination therapy at both doses resulted in better improvements in PEFR and FEV_1 and better symptom control but the increased dose of ICS led to larger decreases in exacerbations (49 vs. 26%, $p<0.01$) compared to the low-dose combination therapy (Pauwels *et al.*, 1997). A follow-up observational database study with over 46,000 patients found similar results with the use of increased doses of ICS offering superior protection against exacerbations and hospitalisations (Thomas *et al.*, 2009).

The optimal dose of ICS at which to add a LABA remains unresolved and as such, the step 3 recommendations within BTS/SIGN, GINA and NHLBI are different.

1.6.3 Efficacy of inhaled corticosteroids in COPD

Traditionally, the treatment of COPD was dependent on the use of bronchodilator therapies. The use of ICS for asthma prompted interest in this therapy for COPD, despite the inflammation in COPD being thought to be largely unresponsive to corticosteroids (Barnes, 2006). Nonetheless, ICS have been used for the treatment of COPD for several decades, much of that time with no evidence base for their use. In the late 1990s, several studies sought to provide support for the use of ICS, but produced mixed results. High doses of budesonide (greater than or equal to 800 micrograms daily) failed to show appreciable or sustained improvement in lung function against placebo over a three-year time period (Pauwels *et al.*, 1999; Vestbo

et al., 1999). However, similar studies of high-dose fluticasone (1,000 micrograms daily) demonstrated a reduction in exacerbation rates, slower decline in health status and better symptom scores (Burge *et al.*, 2000; Paggiaro *et al.*, 1998). With these indications of beneficial effect in COPD, further studies sought to evaluate the best place in therapy for ICS, such as in combination with bronchodilators.

The TRISTAN (TRial of Inhaled STeroids ANd long-acting β_2 agonists) study found that combination therapy with fluticasone/salmeterol reduced the total exacerbation rate compared to placebo (0.97 vs. 1.30 per patient per year, p=0.003), but had no greater effect than treatment with salmeterol or fluticasone alone (1.04 or 1.05 per patient per year, respectively) (Calverley, Pauwels*, et al.*, 2003). However, fluticasone/salmeterol resulted in higher increases in FEV_1, fewer symptoms and less use of relief medicines when compared to its individual components. The Towards a Revolution in COPD Health (TORCH) study subsequently confirmed the benefits of combination therapy in terms of reduction in exacerbations (Calverley *et al.*, 2007). However, fluticasone/salmeterol only reduced rates of exacerbations requiring corticosteroids (termed 'moderate') and not exacerbations requiring hospitalisation (termed 'severe') over salmeterol or fluticasone alone. Additionally, mortality rates were no different for patients treated with placebo, salmeterol, fluticasone, or combination with fluticasone/salmeterol at 15.2%, 13.5%, 16.0% and 12.6%, respectively. The INSPIRE (Investigating New Standards for Prophylaxis in Reducing Exacerbations) study compared combination therapy with fluticasone/salmeterol with tiotropium and found similar rates of overall exacerbations, albeit those requiring antibiotics were more frequent in the fluticasone/salmeterol group and those requiring OCS more frequent in the tiotropium group (Wedzicha *et al.*, 2008). Patients treated with fluticasone/salmeterol had a lower mortality rate (3 vs. 6%, p=0.032) and lower drop-out rates (34.5 vs. 41.7%, p=0.005) than patients treated with tiotropium.

Despite some conflicting evidence, it is generally accepted that ICS therapy leads to a reduction of exacerbations in patients with COPD. Trials evaluating ICS therapy in COPD have overwhelmingly selected patients with moderate to severe disease. Based on a lack of evidence for efficacy above this threshold, the Scottish Medicines Consortium (SMC) currently only recommends combination therapy with

ICS/LABA for the treatment of COPD in patients with an FEV_1 less than 50% predicted with a history of exacerbations (Scottish Medicines Consortium, 2013).

1.6.4 Pneumonia and inhaled corticosteroids

The widespread use of ICS in clinical trials and practice has revealed an important trade-off with their efficacy: an increased risk of pneumonia. This effect was originally detected as an adverse event in the efficacy trials evaluating ICS for the treatment of COPD. In the TORCH study, patients receiving an ICS either by fluticasone alone or with fluticasone/salmeterol were more likely to develop pneumonia (18.3% or 19.6%, respectively, compared to 12.3% for placebo, $p<0.001$). Similar findings were evident in the INSPIRE study with 8% of patients on fluticasone/salmeterol and 4% of patients on tiotropium experiencing pneumonia ($p=0.008$). A post-hoc analysis of the TORCH data also demonstrated that the risk of pneumonia correlated with airflow limitation, with the probability of pneumonia at 15.3% and 29.8% for fluticasone/salmeterol treatment in patients with an FEV_1 of greater than or equal to 50% and less than 30%, respectively (Jenkins *et al.*, 2009). A follow-up meta-analysis of nearly 17,000 patients confirmed the increased risk of pneumonia associated with ICS (RR 1.60, 95% CI: 1.33-1.92) but showed no effect on mortality (RR 0.96, 95% CI: 0.86-1.08) (Singh *et al.*, 2009). However, the included trials were efficacy studies not specifically powered to detect pneumonia-related events.

The majority of studies reporting an increased risk of pneumonia have focused on fluticasone/salmeterol and have not evaluated whether this is a class-wide effect. A meta-analysis of seven clinical trials failed to detect any increased incidence of pneumonia with budesonide compared to controls, but again included inadequately powered studies (Sin *et al.*, 2009). Most recently, the PATHOS analysis demonstrated with a propensity-matched retrospective cohort a higher risk of both pneumonia (rate ratio 1.73, 95% CI: 1.57-1.90) and pneumonia-related death (hazard ratio 1.76, 95% CI: 1.22-2.53) associated with fluticasone/salmeterol compared to budesonide/formoterol (Janson *et al.*, 2013). No dose-response relationship was seen for the risk of pneumonia with either combination. Why fluticasone may cause more pneumonia-related events compared to budesonide is unknown but it may relate to its higher immunosuppressive potency or longer

persistence in the airways due to its relative lipophilicity (Dalby *et al.*, 2009; Ek *et al.*, 1999).

The risk of pneumonia from ICS therapy appears to be isolated to patients with COPD. A retrospective analysis of trials involving budesonide treatment for asthma detected a decreased risk of pneumonia compared to placebo (0.5 vs. 1.2%, $p<0.001$) (O'Byrne *et al.*, 2011). It is hypothesised that the stable and progressive airflow limitation as well as colonisation of bacteria in the lungs is what makes only patients with COPD susceptible to pneumonia (Monso *et al.*, 1995).

1.7 Databases

1.7.1 Relational databases

The concept of the modern relational database was first conceived by British mathematician turned International Business Machines (IBM) Corporation computer scientist Edgar F. Codd, who published *A Relational Model of Data for Large Shared Data Banks* (Codd, 1970); this model suggested that data should be represented as isolated tuples (rows) grouped into relations (tables), with provision of a declarative means to access data. Although the idea was originally rejected by IBM and it took years before the theory was engineered into a product (Clarke, 2013), Codd continued to develop the theory and eventually defined a set of thirteen rules which define the requirements of a relational database management system (RDBMS) (Codd, 1985a; Codd, 1985b). Ironically, none of the major commercial RDBMS in use today fully adhere to all of the rules proposed by Codd, but his work remains the foundation of modern database structures.

Relational databases, by definition, adhere to the concept we now know as ‘normalisation’, or the process of reducing redundancies and dependencies within the dataset (Codd, 1970; Codd, 1972). Presently, there are six levels of normal form (NF) that have been defined, although adherence to the first three proposed by Codd is considered to be sufficient to produce a well-designed relational database structure. For a database to be considered in first normal form (1NF), rows in the table must be non-duplicated, and fields must have only atomic values, or values that are non-divisible; this step is often achieved through the use of at least one unique identifier (or ‘key’) in the table. Second normal form (2NF) states that

attributes should be fully dependent on the unique identifier(s), and third normal form (3NF) requires that no attributes are transitively dependent on the unique identifier. For instance, a user may have a spread sheet with several columns of data pertaining to patients within a GP practice and their associated clinical data (Figure 1.4). *Table1* is not considered in 1NF due to a lack of a unique identifier and the combination of both practice and patient information, which can be achieved by separating it into *Table2* and *Table3*, which use *PracticeID* and *PatID* as their unique identifiers, respectively. *Table3*, although now in 1NF, has attributes (*Height*, *Weight* and *BMI*) which are only dependent on half of the unique key (*PatID*) and therefore violate 2NF. This is addressed by splitting diagnosis and visit information into two separate tables, *Table4* and *Table5*, respectively. Lastly, *Table4* has an attribute (*BMI*) that is transitively dependent in that it is only dependent upon the *PatID* as a function of *Height* and *Weight*. Accordingly, this attribute should be removed from the database as it can be calculated during analysis. The final result is a transformation of the original *Table1* into three separate and normalised tables – *Table2*, *Table5* and *Table6*.

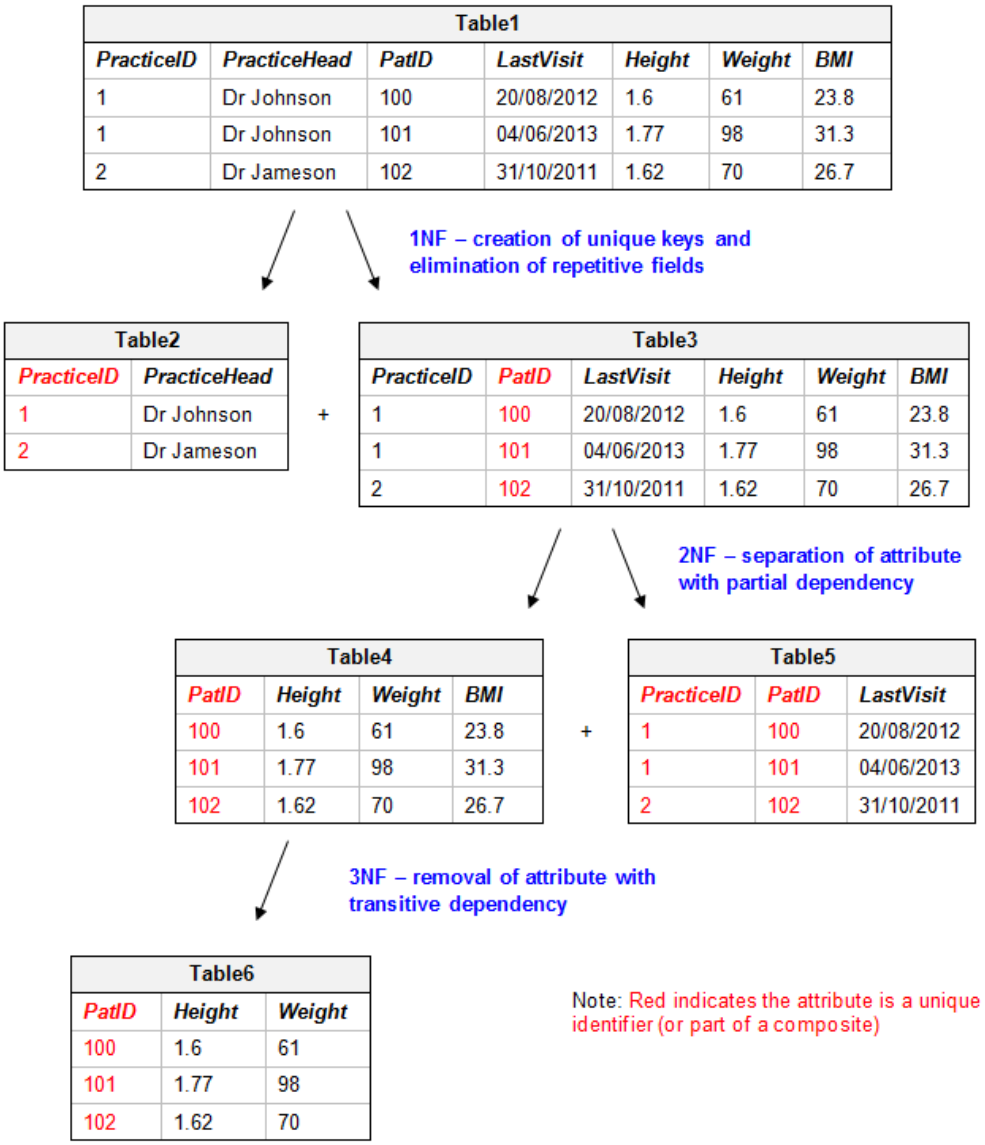


Figure 1.4: Example of the database normalisation process

Database normalisation carries with it several benefits. On the technical side, removing redundancies from data allows for smaller file sizes, less space needed for storage and better indexing capabilities, which can be important for large commercial data warehouses. Normalisation also allows the user to maintain the integrity of the database when adding, changing or deleting data. In the example (Figure 1.4), if *PatID* = '*102*' was removed from *Table1*, this would also result in the removal of *PracticeID* = '*2*' since this is the only recorded patient for the practice at this time. However, in the normalised form of the database, removal of *PatID* = '*102*' from *Table5* and *Table6* has no effect on *PracticeID* = '*2*'.

1.7.2 General approach to data mining

Knowledge discovery in databases (KDD) is the process of transforming simple data into valuable knowledge (Fayyad *et al.*, 1996). Due to the advent of relational theory, databases are able to store and organise large amounts of data, although without the appropriately applied algorithm, no useful information can emerge. KDD is a multi-step process that develops utility from datasets, and broadly encompasses the following (Fayyad *et al.*, 1996):

(1) Development of goals
(2) Selection of the appropriate data set
(3) Pre-processing/cleaning of the data
(4) Selection and execution of data mining methods
(5) Interpretation and validation of resulting patterns

The success of KDD is dependent on the formulation of specific research questions and access to an appropriately suited dataset. Once these are established, useful information can be found. Several methods can be used (Table 1.6).

Table 1.6: Methods of data mining utilised in KDD
Adapted from (Fayyad et al., 1996; Kantardzic, 2003)

Method	Description	Example in respiratory disease
Classification	Categorisation of data into one or more pre-specified classes	Stage of COPD severity
Regression	Fitting of data into a predictive variable outcome model	Receipt of spirometry based on patient characteristics
Clustering	Description of data within finite (non-pre-specified) categories	Geographic trends in tiotropium
Summarisation	Compact description of data	Median FEV_1
Dependency modelling	Description of structural and quantitative dependencies	Association of ICS use with exacerbation rate
Change and deviation detection	Detection of changes in data	Increase in smoking cessation with counselling and pharmacotherapy

The final step of KDD requires the formulation of conclusions and ultimately the generation of goals for future data mining. Conclusions must be considered in the context of several issues, including the influence of missing and noisy data, the assessment of statistical versus real world significance and how applicable the data are to others (Fayyad *et al.*, 1996).

1.7.2.1 Data mining in healthcare

The use of databases for healthcare research is a relatively recent trend, widely expanded by the use of electronic health records (EHR) in healthcare. While RCTs remain the gold standard for evaluating the safe and effective use of medicines, database studies provide a way to study large populations of patients often poorly represented in RCTs, such as the elderly, children or those who are socioeconomically disadvantaged (Schneeweiss *et al.*, 2005).

Databases used in healthcare research are of several forms. Research databases are designed with such purpose in mind and therefore collect detailed data across multiple settings targeted to answer a specific question. However, research databases are generally the result of prospective planning, limiting their implementation logistically and economically. Administrative databases contain data collected during the delivery of patient care, commonly for payment of medical and prescription services. Data fields are limited and grouped under generalised codes and the ability to validate their accuracy is constrained (Shlipak *et al.*, 2005). Lastly, medical record databases are created from data generated in the provision of patient care. While they are privy to large amounts of patient-oriented clinical data (including social history and laboratory results), they may fail to capture the full scope of a patient's treatment through multiple providers and levels of care (Hennessy, 2006). Accordingly, consideration of the type of database is an important step in the KDD process in the realm of healthcare.

Clinical and epidemiological database research has been named as an important area of focus and investment for the future of healthcare research in both Scotland (Scottish Government, 2009) and the USA (Agency for Healthcare Research and Quality, 2012). In the UK as a whole, the Administrative Data Taskforce was created in 2011 as a collaborative effort between the Economic and Social Research

Council, the MRC and the Wellcome Trust. Among their goals is the establishment of administrative data research centres in each of the four countries of the UK to "*provide a robust UK-wide evidence base to inform research, thereby guiding the development, implementation and evaluation of policy*", of which health-related data plays a significant role (Administrative Data Taskforce, 2012).

1.8 Overall aim and objectives

The overall aim of this thesis was to describe and where appropriate, compare the trends in the pharmacological treatment of asthma and COPD in the UK and USA. Specific objectives of the project were to:

- Assess utilisation of respiratory medicines across Scotland and how treatment patterns within NHS Forth Valley compare to Scotland at-large;
- Evaluate respiratory medicine utilisation within NHS Forth Valley and Kentucky against recommended therapy in clinical treatment guidelines;
- Examine the use of inhaled corticosteroids in patients with asthma or COPD as a function of dosing and place in therapy.

The aim and objectives will be further expanded at the start of each main chapter.

Chapter 2:

Materials and methods

2.1 Data source descriptions

2.1.1 Forth Valley (FV) database

In 2007, the NHS Forth Valley Airways Managed Clinical Network (MCN) received funding from the Scottish Government to incentivise GP surgeries to install and use the Campbell Software Solutions© E-PRS software tool for the capture of clinical data for patients on COPD practice registers (O'Hara, 2011). Although the original focus of the project was quality improvement in COPD, the software was also developed to include asthma as a secondary goal. At the practice level, E-PRS was developed to allow GPs to audit important clinical and prescribing data for their patients but the ultimate goals of this data collection at the health board level were to evaluate clinical guideline use, guide education efforts, and provide information on the needs of respiratory patients and future service development within the MCN (MacKinnon *et al.*, 2009). It was subsequently installed at 46 practices (out of 57 total practices [80.7%] within the health board) and integrated directly with the practice administrative software in use at the time (General Practice Administration System for Scotland [GPASS]). Practices were informally evaluated for representativeness of the health board at-large in terms of size, geographic spread and socioeconomic deprivation, and were determined to be an adequate sample. As of mid-2010 and with the phase-out of GPASS from the health board, active data collection by E-PRS ceased. Aggregated and anonymised data from all participating practices were exported to the Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS) and form what is hereafter referred to as the 'FV database'.

The core of the database was a set of tables with data on the participating GP practices (*tbl_practices* and *tbl_practice_imports*), further subdivided by diagnostic practice registers for both asthma and COPD (Figure 2.1). Patient data (*tbl_asthma_data*; *tbl_copd_data*) were derived from appointments with the GP surgery and included varied data on demographics, spirometry, vaccinations, exacerbations and symptom control. Although no specific encounter dates for patient visits were included within the database, the approximate date of data entry was able to be estimated through use of other surrogate date fields within the table; this was achieved primarily using the export date on which data was downloaded from the E-PRS tool, which occurred on a regular and frequent basis. However, this meant that any work with temporal associations dependent on patient encounter

dates would be skewed forward approximately 1-2 months. Data on issued prescriptions (*tbl_asthma_prescriptions*; *tbl_copd_prescriptions*) were formed from a pre-specified list of medicines mapped from GPASS to the database by Campbell Software Solutions© and contained inhaled and oral therapies pertinent to the care of asthma and/or COPD, including SABA, SAMA, ICS, OCS, LABA, LAMA, theophylline and antibiotics. Specific medicines included in each analysis are detailed in Methods sections of chapter 4 (sections 4.2.1, 4.3.1 and 4.4.1) and chapter 5 (sections 5.2.1, 5.3.1 and 5.4.1). Each prescription data entry included medicine name, strength, quantity, dose, frequency of administration, interval of use, and date issued (which was specifically recorded, unlike the previously mentioned encounter dates). Of note, data on LTRA were not included in this mapping and therefore are not available within the database. Data were limited to that which were collected during the time the E-PRS tool was active, although the tool imported some data prior to 2007 for events where a historical date might be pertinent, such as a patient's diagnosis date or their last recorded spirometry. A summary of pertinent available fields in the FV database is contained in Appendix I.

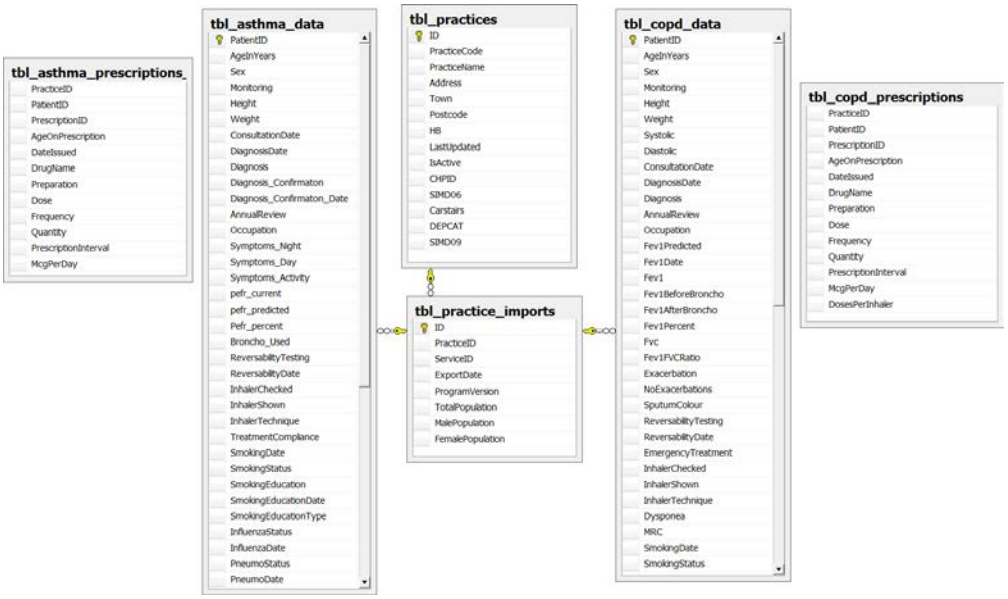


Figure 2.1: Diagram of the FV database structure (selected tables)

2.1.2 Kentucky (KY) database

The University of Kentucky (UKY) Center for Clinical and Translational Science (CCTS) provided access to a subset of the United Healthcare i3 database, which is a large, de-identified, commercially insured database population with dependents. Unlike publicly funded insurance systems like Medicaid (which provides primarily for the socioeconomically disadvantaged) and Medicare (which provides primarily for the elderly) in the USA, the i3 database includes patients with private-pay insurance coverage which would likely be obtained either through full-time employment benefits or individual out-of-pocket payment. The database encompasses 15 million annual insured lives across the USA and provides demographic, medical and pharmacy claim information available for a wide range of diagnosis codes. Data were available for 2007 to 2009 and through a research partnership with the CCTS, a data extract was provided for the present research. Patients were limited to those with geographic residence within the state of Kentucky and one or more qualifying medical claims with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnosis code for asthma, COPD, chronic bronchitis or emphysema (493.xx, 496.xx, 491.xx or 492.xx, respectively). Limited demographic information including year of birth and sex was provided; prescription data (on or after the date of a qualifying medical claim) were isolated to researcher-selected medicines of interest, and included all preparations available on the USA market comparable to those medication classes available in the FV database, with the addition of LTRA. This data formed the basis of what is referred to as the 'KY database'.

The core of the KY database was formed by a general patient table (*Overall*), and complimented by the *Demographics* and *Prescriptions* tables (Figure 2.2). Patients were attached to their relevant diagnosis through the *Indicator* table. Historical data were not available for any fields. Specific medications are detailed in Methods sections of chapters 4 and 5. A summary of comparable fields in the KY database is contained in Appendix I.

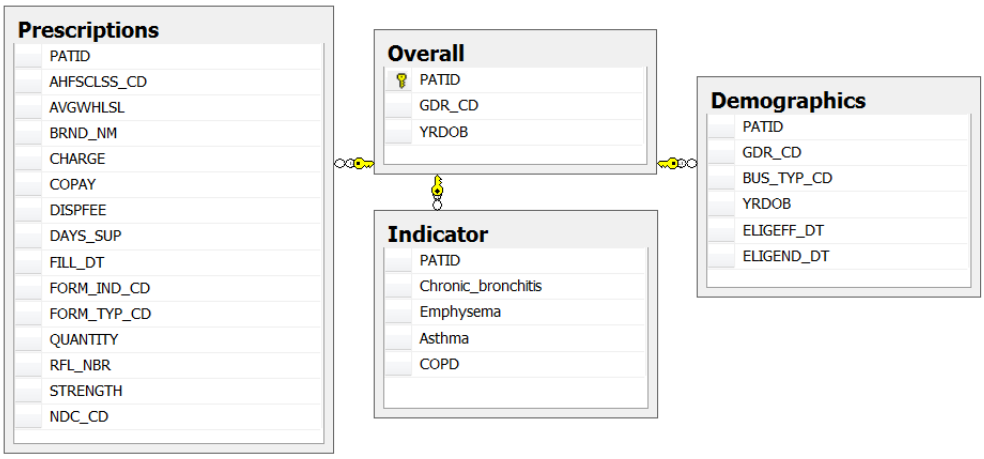


Figure 2.2: Diagram of the KY database structure (selected tables)

2.1.3 Prescribing Information System (PIS) database

The Prescribing Information System (PIS) is the complete national prescribing dataset for Scotland held by National Health Service (NHS) Scotland National Services Scotland (NSS). The 'PIS database' was created from information supplied by the Practitioner Services Division of NSS, who are responsible for the processing and pricing of all prescriptions dispensed in Scotland. Through a second research partnership, colleagues at NHS NSS Information Services Division (ISD) coordinated access to PIS database. Data were available from 2002 to present day (minus a lag period in the most recent quarter), including fields for a variety of metrics, including prescriber and dispenser information (location, organisational structure) and prescription details (medicine name, strength, formulation, and cost). Reliable patient-oriented data (age, sex, location, and socioeconomic deprivation indices) was available approximately beginning in the 4th quarter of 2009, when the Community Health Index (CHI) capture rate on prescriptions processed through NHS NSS averaged over 95% (McTaggart, 2012).

2.1.4 Data use and ethics approval

Use of the FV database was coordinated through a verbal agreement with the NHS Forth Valley Airways MCN; SIPBS departmental ethics determined that no formal review of the project was required (Appendix II). Access to the KY database and the PIS database were arranged with data use contracts with the University of Kentucky

and NHS Scotland, respectively (Appendix II). Ethics approval was included in each data use contract under blanket approval for researchers affiliated with each respective institute.

2.2 Data access

2.2.1 Hardware/software

Both the FV and KY databases were stored on a secure password-protected server using SQL Server 2008® Developer Edition (Microsoft Inc.; Redmond, WA). The KY database was initially accessed through the use of a virtual private network (VPN) connection with CCTS; a subsequent change in privacy agreement between CCTS and their data vendor later enabled a full download of the KY database to the home server without the use of a VPN. The server was hosted on a Dell Optiplex™ 780 32-bit operating system with 4 gigabytes random access memory (RAM) and Intel® Core™2 Duo central processing unit (CPU). The PIS database was accessed through Business Objects™ XI (SAP AG; Walldorf, Germany), a web-accessed enterprise data warehouse programme. Access was limited to use on NHS-networked machines within their firewall and security framework.

2.2.2 Structured query language

Structured query language (SQL) is a programming language used to access RDBMS. Data are stored in a series of interrelated tables and operations are performed using SQL statements, which are broadly separated into those which retrieve data (called ‘queries’), or those which manipulate data in the database. Each statement is composed of several clauses, which form the components of an SQL statement, and predicates, which limit conditions of the data return.

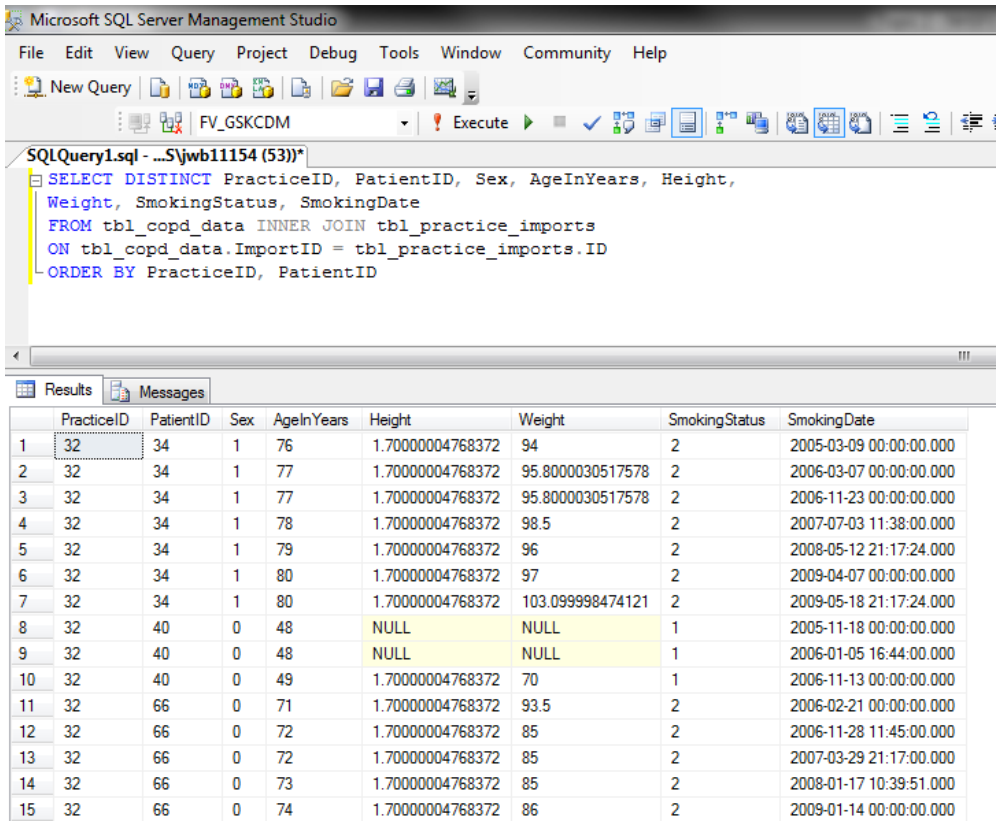
Four basic clauses are central to query statements: specifying which attributes the user wants to access (*SELECT*), where the attribute is located (*FROM*), the constraints the user wishes to put on the data return (*WHERE*), and the sorting of the data for viewing (*ORDER BY*). The *DISTINCT* qualifier is used in combination with *SELECT* to eliminate duplicate entries. Data fields in the *SELECT* clause can be manipulated using aggregate functionalities, such as producing averages, counts or finding extremes of a specified attribute (*AVG*, *COUNT* or *MAX/MIN*,

respectively); these functions are used in combination with the *GROUP BY* clause to specify the conditions on which the aggregation is meant to occur. *CASE* statements are used within the *SELECT* clause to evaluate a set of conditions and a specified return (using an *IF*…*THEN* syntax). Queries are limited in some circumstances by the data type, which specifies the kind of data the attribute holds (numeric, date/time, character strings). Fields containing no data appear blank or are designated as *NULL*; these denotations are present in both the raw database structure or can be returned as the result of a query statement. As query statements simply access data, no change is made to the underlying database structure through their use. However, their results may differ if the data are altered between successive queries.

Data manipulation statements enable the user to modify, add and remove data from the database using functions such as *UPDATE, CREATE* and *DELETE*, respectively. Both individual attributes and entire table structures can be manipulated either in whole or in part by conditional specification with a *WHERE* clause. A manipulation statement affects a permanent change to the database structure without an 'undo' capability ('non-reversible computing').

SQL statements (both queries and manipulations) are entered into a text panel generally without regard to whitespace. After statement execution, results of the statement are displayed in a lower panel with selected attributes as columns, and data entries as rows (Figure 2.3). Each row represents a single entry record in the database for either individual patient or a prescription and is distinguished through the use of a unique key. Patients in the FV database were assigned a unique key combination of two identifiers – *PracticeID* and *PatientID* (within *tbl_practice_imports* and either *tbl_asthma_data* or *tbl_copd_data*, respectively). Use of either of these identifiers without the other would result in a query return listing multiple patients: two patients at one practice sharing the same practice code but different patient codes, or two patients from different practices sharing the same patient code, but different practice codes. However, the combination of these two fields allowed for reference of a specific patient across multiple tables in the database. Patients in the KY database were identified through the use of single identifier – *PATID*. In both databases, individual prescriptions were isolated using a combination of the drug

name (*DrugName* in the FV database; *BRND_NM* in the KY database) and the date of issue (*DateIssued*; *FILL_DT*).



	PracticeID	PatientID	Sex	AgeInYears	Height	Weight	SmokingStatus	SmokingDate
1	32	34	1	76	1.70000004768372	94	2	2005-03-09 00:00:00.000
2	32	34	1	77	1.70000004768372	95.8000030517578	2	2006-03-07 00:00:00.000
3	32	34	1	77	1.70000004768372	95.8000030517578	2	2006-11-23 00:00:00.000
4	32	34	1	78	1.70000004768372	98.5	2	2007-07-03 11:38:00.000
5	32	34	1	79	1.70000004768372	96	2	2008-05-12 21:17:24.000
6	32	34	1	80	1.70000004768372	97	2	2009-04-07 00:00:00.000
7	32	34	1	80	1.70000004768372	103.099998474121	2	2009-05-18 21:17:24.000
8	32	40	0	48	NULL	NULL	1	2005-11-18 00:00:00.000
9	32	40	0	48	NULL	NULL	1	2006-01-05 16:44:00.000
10	32	40	0	49	1.70000004768372	70	1	2006-11-13 00:00:00.000
11	32	66	0	71	1.70000004768372	93.5	2	2006-02-21 00:00:00.000
12	32	66	0	72	1.70000004768372	85	2	2006-11-28 11:45:00.000
13	32	66	0	72	1.70000004768372	85	2	2007-03-29 21:17:00.000
14	32	66	0	73	1.70000004768372	85	2	2008-01-17 10:39:51.000
15	32	66	0	74	1.70000004768372	86	2	2009-01-14 00:00:00.000

Figure 2.3: Screenshot of general patient-based SQL query

The *JOIN* function is used to access data simultaneously across multiple result sets, which requires specification of what parameter in each result should be utilised to link data together (using the *ON tableA.parameterA = tableB.parameterA* convention). *JOIN* functions are set to default to an *INNER JOIN*, which returns all rows in both results that have a match (Figure 2.4). Variations such as *LEFT JOIN* or *RIGHT JOIN* return all rows from the result on the specified side of the join and matching rows from the other side of the join, creating *NULL* values when there is no match. An *OUTER JOIN* is a combination of a *LEFT JOIN* and a *RIGHT JOIN* and returns all rows from both result sets. A similar set of commands (*UNION*, *EXCEPT* and *INTERSECT*) also function like *JOIN* in that they combine multiple result sets with the ability to include/exclude overlapping areas.

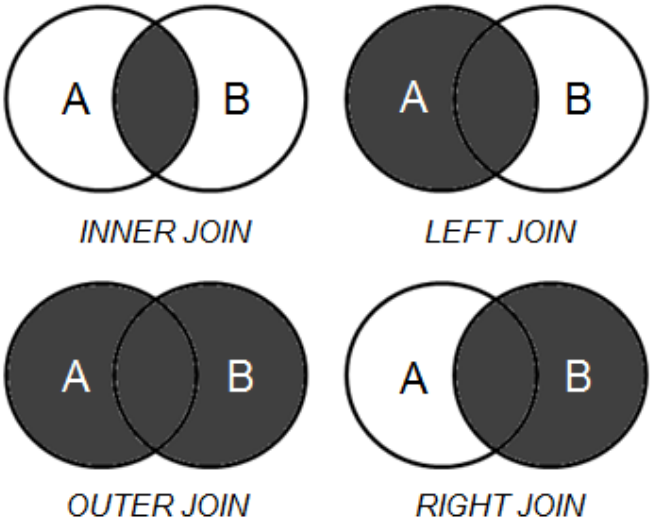


Figure 2.4: Venn-diagram representation of main *JOIN* types

Several other advanced SQL techniques are available, namely the creation of interim tables to utilise in stacked queries. Two techniques – derived tables and temporary tables – embed queries within one another, using the results of one query to limit or build another query. Derived tables create a temporary result set that is purely virtual and exists only within the logical construct of the executed query statement, while temporary tables create a result set that is formally declared and exists within memory until purged.

The SQL syntax used for analyses is referenced throughout the remainder of the text, with samples contained within Appendix III.

2.2.3 Business intelligence platforms

Business intelligence (BI) is a generic and encompassing term referring to all the applications and technologies used to collect, process and transform data for business purposes. Common features of BI software (such as BusinessObjects™ XI) include reporting, data query and analysis, and performance management. Ad-hoc data queries are designed by the user through an object-oriented user interface and a ‘drag-and-drop’ utility, which utilises an underlying SQL syntax without the user possessing the requisite computing knowledge.

When running queries through the web-interface of BusinessObjects™ XI, users are presented a three-part screen including a dual pane for creation of result objects on top and query filters on the bottom, and a side data tab (Figure 2.5). The data tab presents an 'activity universe' or a collection of data classes available to use in query creation. Within each data class is a list of objects, which come in several forms (Table 2.1). Dimension objects form the structure of most queries and contain character-based data and/or dates; detail objects build upon a dimension object and may provide further clarification as to its content. Measure objects provide numerical data often derived from other objects.

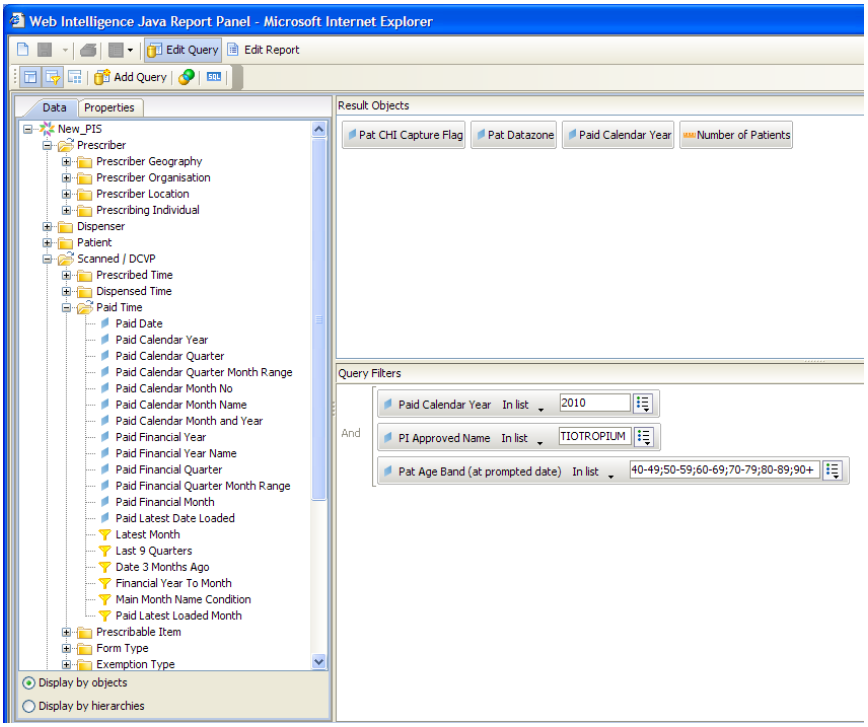


Figure 2.5: Screenshot of general BusinessObjects™ XI query

Table 2.1: Types of objects available in business intelligence

Object	Definition	Examples
Dimension	Basis for query results	Patient Prescription
Detail	Descriptive data regarding a dimension	Age band of patient Date of issue
Measure	Calculated results based on other fields	Number of patients Number of prescriptions

Objects are utilised in the result pane to formulate the intended output of the query, but also in the query filter pane to limit the results, not unlike the specifications made in *SELECT* and *WHERE* clauses, respectively. As in SQL, queries were able to be combined similar to *JOIN* functions, using *INTERSECT*, *UNION* and *MINUS*.

2.3 Data preparation

2.3.1 Cleaning of the FV database

Although SQL is not case-sensitive, it does isolate differences in spelling and syntax when returning query results. Previous research work with the FV database noted that many of the attributes were highly inconsistent due to misspellings, improper syntax and free-text data entry and would require standardisation to gain any meaningful output (Jefferson, 2011). Accordingly, a set of cleaning procedures were executed within the FV database prior to the commencement of any research inquiry.

Each attribute was systematically isolated and ordered using a data retrieval query using *SELECT DISTINCT* and *ORDER BY* functions; the results, showing all unique data entries within a particular attribute, were scanned for inconsistencies in syntax. When duplicates of the same field were discovered, a manipulation statement (using *UPDATE*) was composed to modify the duplicates toward a single form (Table 2.2). After executing the UPDATE statement, the retrieval query was repeated, and the next duplication targeted. After all duplicates had been processed, the retrieval query was executed a final time, and the condensed list of fields within the attribute scanned for any overlooked fields.

Table 2.2: Selected examples of duplicates identified and modified during database cleaning

Attribute	Examples of duplicates	Standardised form
Preparation	200mcg, 200 mcg, 200 mcg inhaler, 200 micrograms, 200mcg/dose	200 mcg/dose
Dose	1-2 puffs, 1-2 sucks, 1-2 doses, 1 – 2 puffs, one or two doses	1 to 2 puffs
Frequency	BD, BDS, BID, twice daily, twice a day, 2 times daily, morning and night	Twice daily
Quantity	100 nebules, 25 x 4, 1 box of 100	100

In addition to varied syntax, there were rows where data mapping failed to place free-texted entries into the correct attributes, resulting in combinations such as *Dose* = '*2 puffs twice daily*' and *Frequency* = '*NULL*', or FEV_1 = '*0.65, predicted 64%*' and FEV_1*Predicted* = '*NULL*'. In these situations, the *UPDATE* function was used to first modify the *NULL* field to include the appropriate information, and then to remove extraneous data from the populated field.

2.3.2 Data completeness and quality of the FV database

To understand the capabilities and limitations of the FV database, an evaluation of data completeness and quality was also conducted using methodologies similar to those established in the previous work with the database (Jefferson, 2011). The FV database contained 53 attributes in *tbl_asthma_data* and 67 attributes in *tbl_copd_data*. Although each row corresponded to a separate encounter with the GP surgery, not all attributes were populated in each row, and their relative completeness among the patient cohort was unknown. Furthermore, as patients had varying numbers of encounters with the GP surgery, the balance of attribute completeness for individual patients was also unknown. Using the *SELECT* (non-*DISTINCT*) function, *PracticeID* and *PatientID* were queried to determine the number of rows in the data tables for each diagnosis. Each attribute of interest was added separately to this base query, with the specification that the attribute *IS NOT NULL*; this provided the number of populated rows for each attribute. A second query of *PracticeID* and *PatientID* was formed, using the *SELECT DISTINCT* function to determine the number of individual patients within each table. This was linked via a *LEFT JOIN* to the first query to determine the number of populated patients (the number of patients who had at least one data entry) for each attribute. Several attributes were queried jointly, as their information was interdependent, such as a status and the date the status was assessed.

The results of this evaluation (Table 2.3) show that attributes in the COPD table were relatively more complete than those in the asthma table; this was anticipated as these patients were the primary focus of the original clinical project with the MCN. Row and patient completeness was of similar proportions between groups, meaning that attribute recording was evenly distributed amongst the database. Age and sex

were available for all patients in both the asthma and COPD tables, as was diagnosis date for the COPD table. Some fields in the asthma table had low levels of patient completeness (less than 50%) including symptoms, pneumococcal status and reversibility testing, although the latter two were likely a function of the attributes only being pertinent in special clinical situations. All attributes in the COPD table had high levels of completeness; although FEV_1 and *FVC* were poorly completed across rows, most patients had at least one recorded entry overall.

The analysis also shed light on the fact that multiple data entries per patient were available for many data fields. Although these fields were easily able to be amalgamated with SQL syntax when they appeared as simple duplicates, several fields also contained time-dependent attributes, such as a non-smoker becoming a smoker, or lung function as measured by spirometry declining over time. Although these cases were found infrequently within the time frame of analyses conducted, these situations were handled assuming 'worst case scenarios' where the most extreme value amongst a grouping of attributes was utilised as the singular cross-sectional value for a patient. This technique incurs a certain degree of limitation as it fails to incorporate how changes in these variables may change the effect on outcomes over time; this could be overcome through the incorporation of other techniques such as marginal structure models, although not included in the present body of work.

Table 2.3: Completeness of selected attributes in the FV database

Attribute	Asthma, n (%)		COPD, n (%)	
	Rows	Patients	Rows	Patients
Sex	57,274 (100.0)	17,611 (100.0)	24,026 (100.0)	5,874 (100.0)
Age	57,273 (100.0)	17,611 (100.0)	24,026 (100.0)	5,874 (100.0)
Height	51,350 (89.7)	15,789 (90.2)	22,614 (94.1)	5,567 (94.8)
Weight	45,364 (79.2)	14,454 (82.1)	22,603 (94.1)	5,575 (94.9)
Diagnosis date	29,227 (51.0)	9,469 (53.8)	24,026 (100.0)	5,874 (100.0)
Smoking status/date	54,460 (95.1)	16,715 (94.9)	23,932 (99.6)	5,844 (99.5)
Influenza status/date	46,906 (81.9)	14,047 (79.8)	19,221 (80.0)	5,445 (92.7)
Pneumococcal status/date	20,324 (35.3)	6,341 (36.0)	18,880 (78.6)	4,751 (80.9)
Reversibility testing/date	3,157 (5.5)	1,233 (7.0)	12,793 (53.2)	4,705 (80.1)
Inhaler technique/date	46,315 (80.9)	14,103 (80.1)	19,764 (82.3)	4,844 (82.5)
Symptoms (day/night/activity)	11,153 (19.5)	6,022 (34.2)		
PEFR current	44,960 (78.5)	13,716 (77.9)		
PEFR %	30,063 (52.5)	9,585 (54.5)		
MRC score			7,303 (30.4)	3,797 (64.6)
FEV_1			7,974 (33.2)	5,792 (98.6)
FVC			5,387 (22.4)	5,758 (98.0)
FEV_1 % predicted/date			18,936 (78.8)	5,052 (86.0)

After assessing completeness, data were then assessed for quality. Each attribute by itself was isolated using *SELECT DISTINCT*, and using the *ORDER BY* function, the list of entries was sorted and subjectively scanned for outliers and/or entry errors. Expected values for attributes were defined *a priori* and an error percentage calculated as a function of the number of outside the expected range divided by the

total number of specified attribute rows. Several types of data quality issues were identified (Table 2.4). More issues were identified for age and weight attributes in the COPD table compared to the asthma table. Outliers identified in the height and weight attributes were thought to be the result of incorrect units for measurement (height in centimetres instead of metres, weight in pounds/stones instead of kilograms). Erroneous date attributes resulted from the use of non-existent dates such as years 1899 or 2098 – likely as placeholders if the date was unknown to the clinician during the encounter. Some extreme values were also found in attributes detailing lung function test results (*PEFR*, FEV_1, *FVC* and FEV_1 *% predicted*), such as very low values, or percentages outside of the 1 to 100% range; however, delineating between possible errors and true values was less clear in these situations.

Table 2.4: Quality of selected attributes in the FV database

Attribute	Example	Asthma, n (%)	COPD, n (%)
Age	Less than 40 (COPD) Greater than 100 (both)	2 (<0.001)	74 (0.3)
Height	Less than 1.4 metres (COPD) Greater than 2 metres (both)	350 (0.7)	178 (0.8)
Weight	Less than 40 kilograms (COPD) Greater than 135 kilograms (both)	455 (1.0)	374 (1.7)
Dates (all)	Earlier than patient birth (both) Later than 2010 (both)	483 (<0.001)	454 (<0.001)

As a subjective assessment, it is important to note that not all rows identified were necessarily true errors, nor were all erroneous fields in the database identified. However, with relatively stringent expected values, the resultant error rate in the database was minimal, and the data assessed to be of sufficient quality for further analysis.

2.3.3 Cleaning/quality of the KY and PIS databases

As administrative databases, the KY and PIS databases were not subject to the same issues regarding data quality and were fit for purpose at initial access. Accordingly, no cleaning procedures were required or executed.

Chapter 3:

Respiratory disease in Scotland

3.1 Introduction, aims and objectives

National pharmacy dispensing data in Scotland (the PIS database) relating to respiratory medicines in Scotland (not associated with a diagnostic code) were used to first, qualitatively map respiratory disease within the country and secondly, to quantitatively assess 10-year longitudinal trends in medication utilisation. These national data were then compared to regional data for NHS Forth Valley to assess the external validity of analyses within the FV database. The objectives were to:

- Estimate the geographic prevalence of asthma and COPD in Scotland using medication utilisation as a proxy for diagnosis;
- Describe longitudinal utilisation trends for respiratory medicines in Scotland;
- Compare respiratory disease prevalence and medicine utilisation in NHS Forth Valley with the rest of Scotland.

3.2 Intensity mapping

3.2.1 Methods

As no diagnosis data were available in the PIS database, a query was designed to isolate patients in receipt of selected respiratory medications. Objects for *Patient Data zone* and *Number of Patients* were selected, using query filters limiting to *Paid Year* and *Approved Name* (as a detail of *Paid Item*). *Patient Data Zone* referred to the patient's location at the time of the prescription within a geographic boundary as defined by the Scottish Government: 6,505 data zones, each containing approximately 500 to 1,000 residents as estimated by the 2001 Census output (The Scottish Government, 2005). *Paid Year* represented the year that the prescription item was processed and paid by the NHS and was set to 2012. For the COPD query, filters for *Approved Name* and *Patient Age Band* were set to query for tiotropium and age greater than or equal to 40 years old, respectively. For asthma, the filter for *Approved Name* was set to query for all available ICS products (single-agent and combination therapy products in British National Formulary [BNF] section 3.2) and combined via *MINUS* with a second query to exclude patients who had also received tiotropium and were aged 40 years and older in the COPD query. This age constraint was applied to increase the specificity of isolated patients based on the usual diagnostic timeline of COPD discussed in clinical guidelines, which occurs

after 40 years of age based on the timeline needed for cigarette use to induce the functional changes seen in COPD. Mid-year small area population estimates for each data zone were obtained from the General Register Office for Scotland (GROS), using the year prior to receipt of medication – 2011 (General Register Office for Scotland, 2013b). A crude percent prevalence rate for each data zone was calculated as a function of the number of patients who had received the medication(s) of interest (from the PIS database query) divided by the number of patients living in each data zone. Geographic data zone boundaries were obtained from the Scottish Neighbourhood Statistics (SNS) (Scottish Neighbourhood Statistics, 2009) and imported into ArcMap 10 as a shape file (xx.shp). Geographies were linked via data zone code to a comma delimited file (xx.csv) containing the calculated prevalence rates. Intensity maps were generated for each disease, using a quintile grading for prevalence. Higher level geographies were also evaluated, including local authorities (consisting of 32 governmental boundary areas) and health boards (consisting of 14 NHS administrative areas).

Disease prevalence for each practice in the FV database was calculated by dividing the number of people on the practice register with asthma or COPD in 2009 and dividing by the reported patient population from the practice (Appendix III; queries 1 – 3). Each practice was routed to a data zone using boundaries from the SNS, and prevalence estimates for each data zone calculated as an average prevalence of the included practices. Prevalence estimates from the FV database were cross-referenced with those from the PIS database from 2012 and plotted to examine the level of agreement.

3.2.2 Results

National data

Crude asthma prevalence rates ranged from 2.40 to 21.33% among individual data zones, with Garelochhead in Argyll & Bute the lowest and Caithness North East in Highland the highest (indicated by the red circles on Figure 3.1). Mean prevalence according to health board ranged from 12.30% in NHS Greater Glasgow & Clyde to 8.79% in the NHS Western Isles. According to local authority, prevalence ranged from 13.09% in East Dunbartonshire to 9.53% in Perth & Kinross. Grouped areas of increased prevalence were scattered throughout the country, including in local

authority areas of Aberdeenshire, Moray, Eilean Siar, Highland, Argyll & Bute and Dumfries & Galloway. In the central belt of Scotland (Figure 3.2), increased asthma prevalence was concentrated in Glasgow City and nearby areas of North and South Lanarkshire and East Renfrewshire; areas within Falkirk and Stirling also had elevated prevalence rates. Edinburgh and surrounding areas had a consistently low prevalence with the exception of south-east Edinburgh near Niddrie (indicated by the red circle on Figure 3.2).

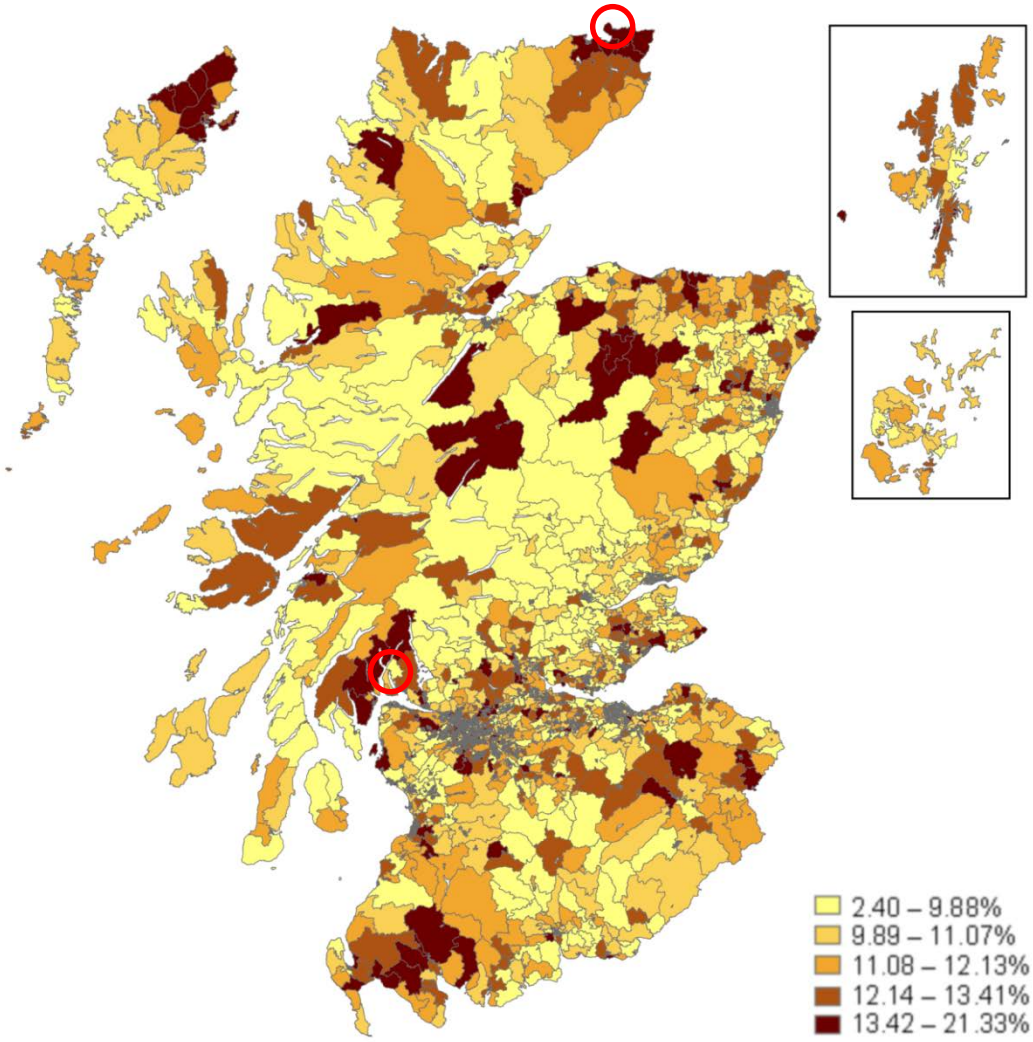


Figure 3.1: Asthma prevalence in Scotland by data zone (2012)

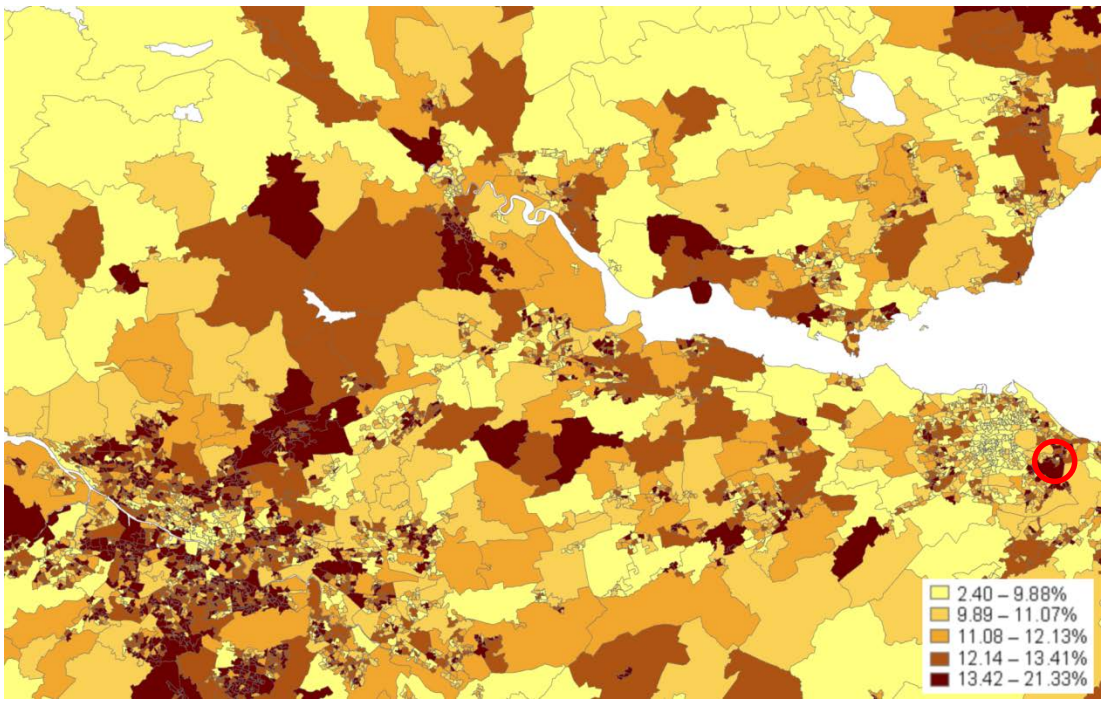


Figure 3.2: Asthma prevalence in the central belt of Scotland by data zone (2012)

For COPD, crude prevalence rates ranged from 0 to 8.63% among individual data zones (Figure 3.3), with 40 data zones failing to identify any prevalence and the highest in Doon Valley South in East Ayrshire (indicated by a red circle on Figure 3.4). Areas with no prevalence were primarily from Lothian and Grampian Health Boards (11 data zones each; 27.5%). Among health boards, mean prevalence was highest in NHS Greater Glasgow & Clyde at 2.09% and lowest in NHS Shetland at 0.56%; among local authorities, prevalence ranged from 2.47% in Glasgow City to 0.56% in Shetland Islands. Nearly all areas with a high prevalence were within the central belt, and centred in Glasgow City, particularly within the eastern and northern areas of the city (Figure 3.4). Other locations with a high COPD prevalence included Moors and Lockerbie in Dumfries & Galloway, Harthill in North Lanarkshire, Stirling and Falkirk (indicated by the red circles on Figure 3.3 and 3.4). The area in and around Edinburgh again had a consistently low prevalence, with the exception of selected areas in the south and south-east part of the city near Niddrie and Wester Hailes (indicated by the red circles on Figure 3.4).

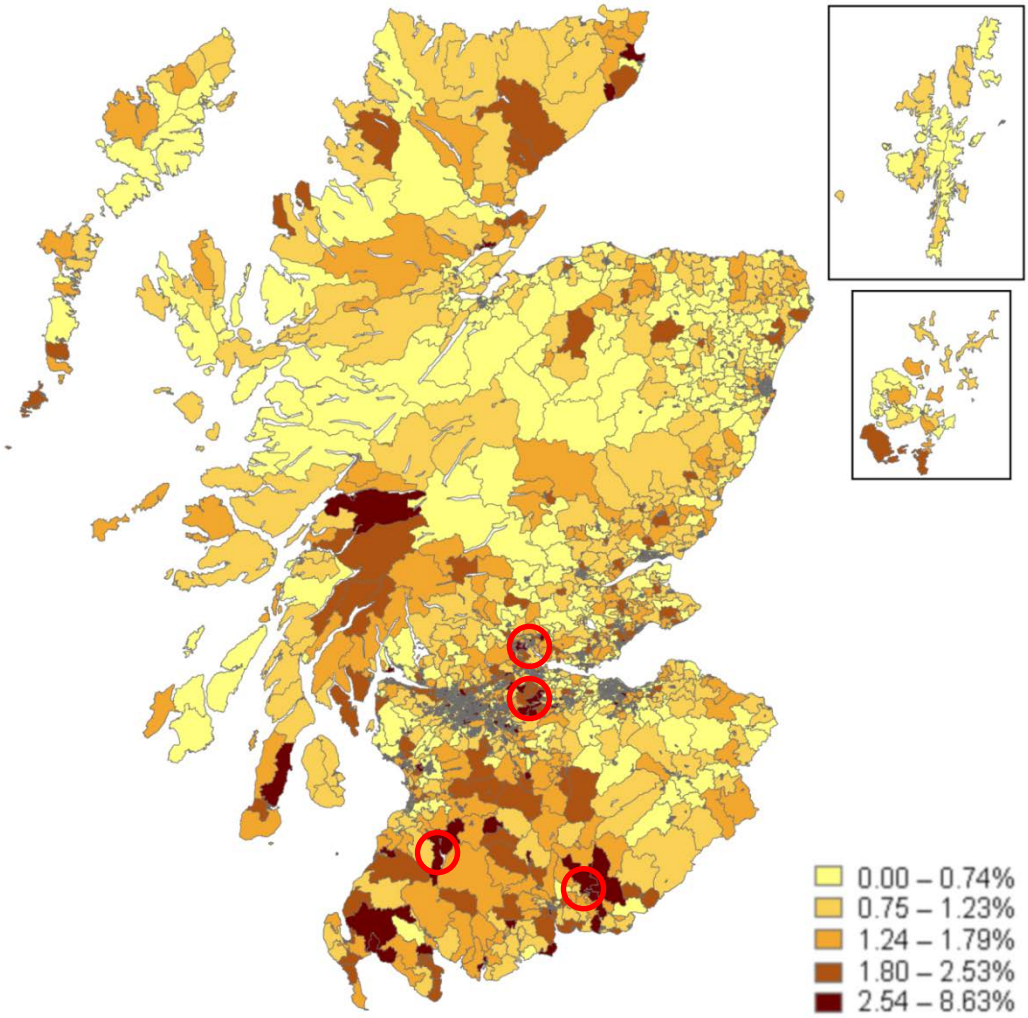


Figure 3.3: COPD prevalence in Scotland by data zone (2012)

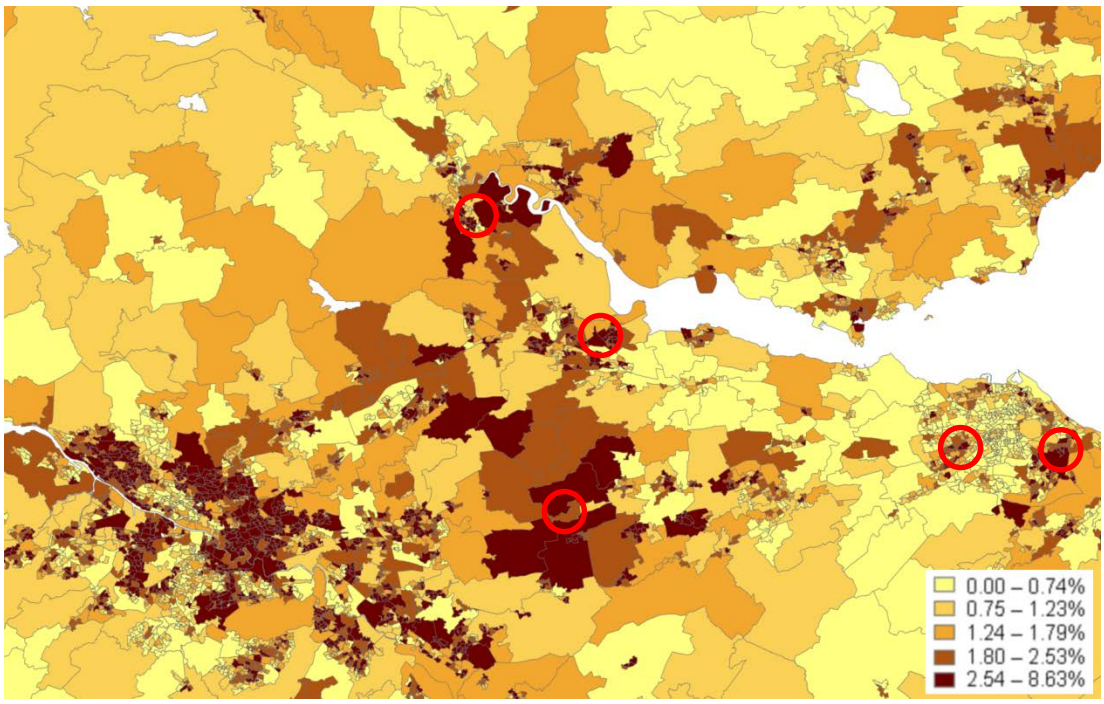
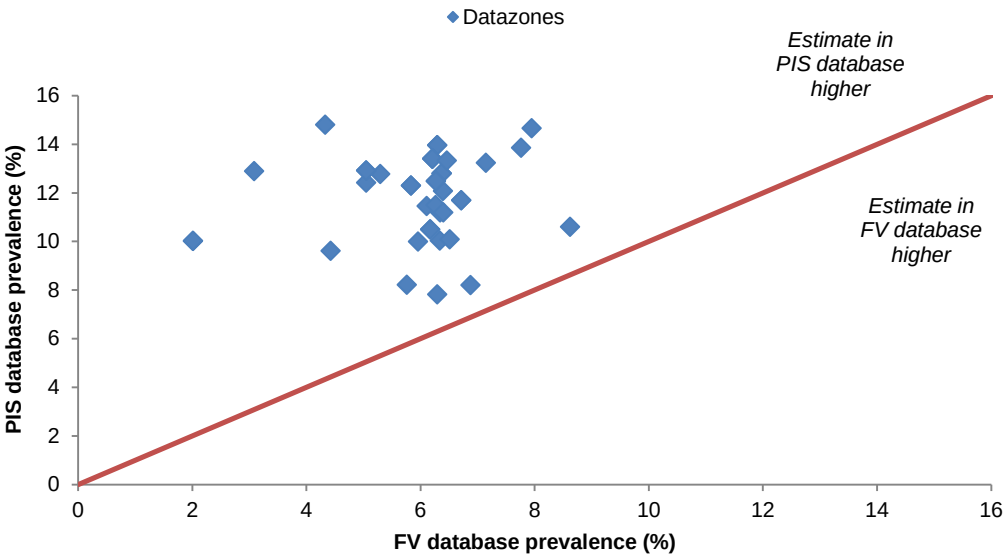


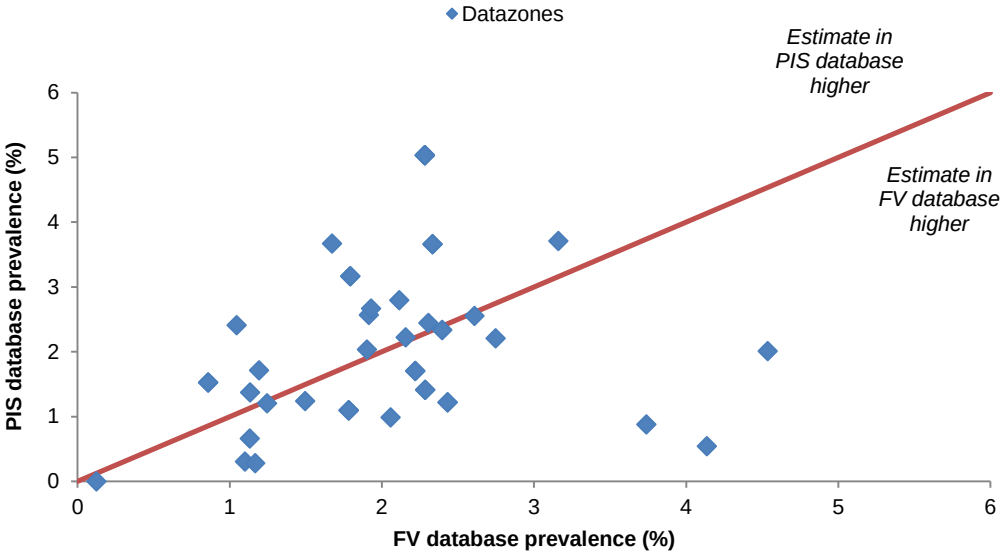
Figure 3.4: COPD prevalence in the central belt of Scotland by data zone (2012)

Regional data

Data were available for 46 practices in the FV database, which were mapped to 32 different data zones. The comparison of data zone prevalence estimates between the PIS and FV databases are shown in Figure 3.5(a) and (b) for asthma and COPD, respectively. For asthma, the PIS prevalence was higher than the FV database prevalence for all of the data zones assessed, with a larger cluster of data zones with FV prevalence estimates near 6.0%, but with PIS prevalence estimates at nearly two-fold higher. For COPD, the prevalence estimates were better aligned, with a higher PIS prevalence in 15 data zones (46.9%). Data zones were primarily between 1.0 to 3.0% for both databases, although several outliers were also present, with the FV database estimating several practices higher than the PIS database.



(a)



(b)

Figure 3.5: Comparison of prevalence in FV database (2009) vs. PIS database (2012) for **(a)** asthma and **(b)** COPD

3.2.3 Discussion

The prevalence distribution of asthma in Scotland was variable, with an absolute differential of nearly 20% across data zones. The prevalence of asthma was sporadically distributed across Scotland, while COPD prevalence was more uniformly found in the central belt around Glasgow and stretching east through Forth Valley. Less densely populated areas of Scotland such as the Highlands and the Islands generally had a lower prevalence of respiratory disease and COPD in particular. Traditionally, people living in rural areas have been thought to have better health, less disability and lower rates of smoking (Scottish Executive, 2003). In specific regard to respiratory disease, location can influence prevalence in several ways.

Among the most common environmental triggers of asthma exacerbations are air pollutants, changes in atmospheric conditions such as increased humidity or cold air, and tobacco smoke (Vernon *et al.*, 2012). Environment may further contribute through increased exposure to allergic triggers, such as for people living in deprived and/or overcrowded housing establishments and their greater exposure to mould, dust mites and cockroaches (Bryant-Stephens, 2009). Urban areas have been thought to contribute to asthma based on environmental conditions but also through socioeconomic determinants that are more prevalent in cities, such as poor access to resources, stress associated with poverty and family dysfunction (Bryant-Stephens, 2009). Increased asthma prevalence in urban areas in Scotland may reflect the effect of these exposures.

It is important to delineate between factors which may cause asthma and therefore increase prevalence, and factors which worsen symptoms of the disease. Allergens may fall under either category, either providing the allergic sensitisation thought to help initiate asthma or by inducing exacerbations from acute and/or chronic exposure. As cities have a high burden of allergens, pollution and tobacco smoke, the correlation of asthma prevalence in urban areas is intuitive. However, other variables can contribute to the cause of asthma such as family history of disease, genetic predisposition, viral infections and bacterial colonisation (Bisgaard *et al.*, 2010). Furthermore, in adults, hormones, exercise, medication use and obesity have also been associated with an increased risk of asthma (de Nijs *et al.*, 2013). These

factors are less related to location and urbanity and therefore may contribute to the sporadic areas of asthma prevalence seen in this analysis.

Due to the direct causative relationship between the development of COPD and smoking, areas with increased smoking prevalence should correlate strongly with areas of high COPD prevalence. Estimated smoking rates in Scotland vary widely among local authorities but are generally higher in urban areas. Glasgow City and nearby areas of West Dunbartonshire and North Lanarkshire rank high on the list at 34.0%, 33.3% and 31.7%, respectively (NHS Health Scotland, 2007); there was correlation in these areas with a high concentration of COPD prevalence.

An additional consideration that may contribute to local respiratory disease prevalence is occupational exposure through inhalation of noxious vapours, gases, dusts and fumes (VGDF). It has been estimated that as many as 19.2% of cases of COPD may be attributed to occupational exposure in the USA working-age population, increasing to 31.1% in people with no smoking history (Hnizdo *et al.*, 2002); similarly 9 to 15% of cases of asthma are thought to be associated with occupation factors (Blanc *et al.*, 1999). In both diseases, exposure to VGDF may contribute either to new cases or exacerbate existing disease. A wide variety of industries have been associated with such exposures, including manufacturing, construction, utilities and mining – all with deep historical roots across Scotland.

Assuming an upper age limit of 80 years during 2012, patients included in this analysis entered the workforce from 1950 onwards. For much of the 20th century, Glasgow was known as the 'workshop of the empire' for its role in in shipbuilding and heavy industries (such as machinery and locomotives) supporting efforts in both of the World Wars (TheGlasgowStory, 2004). Although these sectors experienced decline after the Second World War, manufacturing in the Glasgow area employed over 400,000 people in 1952 (MacInnes, 1995). Steel and iron works were particularly important in the Ravenscraig area of North Lanarkshire, where blast furnaces and integrated production plants were built in the 1950s, earning nearby Motherwell the reputation as 'the steel production capital of Scotland'. The area formed a close relationship with Glasgow, where much of the iron ore was unloaded (Findlay, 2003). Lanarkshire also played a large role in the mining industry, in the middle of a stretch of coalfields across the central belt from Ayrshire through Forth

Valley and Fife. The coal mining industry employed approximately 80,000 people in Scotland when it was nationalised in 1946 (Oglethorpe, 2006). In Forth Valley, approximately 30 collieries were in operation in the 1950s, with those in Clackmannanshire and Stirlingshire employing nearly 8,000 miners (Oglethorpe, 2006). Coal mining across Scotland fell into decline in the latter half of the 20th century and deep mining officially ceased with the closure of the last mine near Kincardine in Fife in 2002 (Royal Commission on the Ancient and Historical Monuments of Scotland, 2011). Although open-cast mining still exists today, the respiratory risk and exposure to VGDF is thought to be significantly less.

The location of Glasgow and surrounding areas on the River Clyde made it an optimal location for industry development and met their need for goods importation/exportation; Forth Valley also fell into this category with its close relationship with the Forth and Clyde Canal and the River Forth. People living in these regions and working in these industries were subject to exposure to a variety of VGDF which may have contributed to the higher prevalence of respiratory disease seen across the area. This is in stark contrast to the majority of Edinburgh, which despite being an urban area, lacks the industrial history seen in western Scotland and demonstrated a low prevalence of both asthma and COPD; this area developed within softer industries during in the 20th century, primarily banking, brewing and printing.

The prevalence estimates and subsequent intensity maps from the PIS database are surrogate representations of disease prevalence. As the database holds no diagnostic information, receipt of respiratory medication was used as an estimation of diagnosis. Tiotropium is currently only licensed for the treatment of COPD and therefore should provide a reasonable diagnostic marker; accordingly, it has been used to isolate probable COPD patients in previous work (Breekveldt-Postma *et al.*, 2007). There has been emerging interest in the use of tiotropium for patients with asthma (Kerstjens *et al.*, 2012), so an age constraint was added to the query to exclude younger patients who might be trialled on tiotropium for asthma based on this new evidence; additionally, the diagnostic and physiological timeline for COPD means that patients are rarely diagnosed prior to 40 years of age. There remain significant limitations to using pharmacy data as a surrogate diagnostic marker. First, patients with mild symptoms of either disease who were treated only with

short-acting therapies like SABA or SAMA were not accounted for. As tiotropium is likely to be a specific but not a sensitive marker for COPD, patients who received other therapies such as ICS/LABA may have been wrongly included within the asthma estimates. Lastly, patients may have received respiratory medications as a diagnostic trial or for reasons outside the licensed indication such as acute bronchitis; these patients would have been wrongly included in the prevalence estimates. Overall, the use of medicine utilisation as a marker for disease prevalence is likely to be a dramatic underestimation, and when other more specific options are available (or combinations of data from multiple sources to better mark diagnosis), they should be preferentially utilised.

The Quality Outcomes Framework (QOF) was established in the NHS as a part of the new General Medical Services (GMS) contract in 2004. As a voluntary incentive programme, QOF offers supplemental income to GP practices in the UK by measuring their achievement against a range of quality and evidence-based indicators in domains related to clinical, administrative and organisational care; one such indicator of quality achievement involves maintaining practice registers of patients with chronic diseases (Information Services Division Scotland, 2013b). QOF estimates of disease prevalence are also subject to limitations, including using unadjusted estimates, having an inability to verify the accuracy of data recording or differences in diagnostic methods between practices and providing an underestimation for diseases where patients fail to consult their GP such as COPD. In 2011/12, practice-level prevalence estimates in Scotland ranged from 2.09 to 13.87% and 0.11 to 7.94% for asthma and COPD, respectively (Information Services Division Scotland, 2013b) – rates broadly (at best) comparable to those estimated by the current analysis.

Prevalence estimates from the PIS database were also compared to those from the FV database. As the FV database and the QOF formulate estimates from practice disease registers, it would not be expected to have perfect agreement with those from the PIS database, which used medication utilisation to estimate prevalence. Further disagreement would be anticipated from the comparison between FV database estimates from 2009 and PIS database estimates from 2012; the timeline of available data from either database prevented comparison of the same year. Nonetheless, the results suggest a number of possible scenarios. The better

agreement of estimates for COPD may suggest that tiotropium is a more specific medication utilisation marker for COPD than ICS is for asthma. It may also suggest that the breadth of data collected for patients with COPD in the FV database was better and more representative. The collection of COPD data was the primary goal of the E-PRS tool and practices may have had more incentive to collect these data, whereas the collection of asthma data was additional, and an underestimation of prevalence may have resulted from not capturing all patient data. None of these measures refers to the quality of the collected data within the FV database but it may indicate that the database only refers to a subset of the patient population with asthma in the health board.

Regardless of method of estimation, as many as 2.8 million people with COPD in the UK remain currently undiagnosed (British Lung Foundation, 2007), primarily because they believe their symptoms to be an expected result of smoking and are unaware that they are an indicator to seek medical treatment. In one analysis, among patients identified with the most severe degree of airflow limitation (FEV_1 % predicted less than 50%), less than half of them had ever been given a respiratory diagnosis (Shahab *et al.*, 2006). Although the deficit is not as drastic, the prevalence of untreated asthma in the UK has been estimated at 1.2 to 2.4% (Dow *et al.*, 2001), with the highest burden seen in elderly patients (Hanania *et al.*, 2011). Accordingly, the true burden of respiratory disease is likely to be higher than found in this analysis or in estimates from data such as QOF.

3.3 Medicine utilisation

3.3.1 Methods

Scotland-wide analysis

Objects were selected for *Health Board Name*, *Month/Year* (detail of *Paid Time*), *Approved Name*, *BNF Item Description* (drug item description with product name, formulation and strength), *Number of Paid Items* (number of prescriptions paid for by the NHS) and *Paid Quantity* (number of units on each prescription; e.g. number of inhalers, nebules or tablets) (NHS National Services Scotland, 2012). A query filter for *BNF Root Drug Description* was selected to specify respiratory medications contained within the BNF chapter on respiratory medicines, including all available SABA, SAMA, ICS, LABA, combination therapy inhalers, LAMA, theophylline and LTRA. A second filter for *Month/Year* limited the results from January 2003 – December 2012, based on availability of data within the PIS database.

Three medicine utilisation metrics were calculated and compared on a monthly basis, including the assumed prescribed daily dose (aPDD), the defined daily dose (DDD) and total items. The aPDD was measured according to a previously published algorithm (Boyter *et al.*, 2005) and calculates utilisation as a function of inhaler size and usual dosing regimen, without regard to dose. Each inhaled formulation was assigned an aPDD factor (the expected number of daily doses) according to formulation type; pMDI formulations were assigned an aPDD factor of 4, while DPI formulations (Accuhaler®, Turbohaler® or Diskhaler®) were assigned an aPDD factor of 2. The total doses for each inhaler were determined according to package size, and adjusted for the aPDD factor according to equation 3.1. As the aPDD factor assumes a usual dosing regimen for inhalers, it was not calculated for inhaled medications delivered by nebuliser, or for oral medications. For reliever inhalers (which are generally dosed on an 'as needed' basis), the same factors were applied according to pMDI/DPI formulation.

Equation 3.1:

$$\text{aPDDs/1,000 people} = \frac{\dfrac{(\text{Number of inhalers} * \text{doses/inhaler})/(\text{aPDD factor})}{30 \text{ days}}}{\text{Total population}} * 1{,}000$$

The DDD is a similar metric for medicine utilisation, which also calculates utilisation as a function of inhaler size, but additionally incorporates the strength of the medicine (in milligrams [mg]) and standardises using a published DDD factor from the WHO database, or the "*assumed average maintenance dose per day for a drug used for its main indication in adults*" (Table 3.1) (World Health Organization, 2013b).

Table 3.1: DDD factors for selected respiratory medications
Adapted from (World Health Organization, 2013a)
† *DDD factor utilised for both single-agent ICS and CMB inhalers*

Medicine	**DDD factor (mg)**	
	pMDI/DPI	**Nebulised**
Salbutamol	0.8	10
Terbutaline	2	20
Ipratropium	0.12	0.3
Beclometasone	0.8	
Budesonide †	0.8	1.5
Fluticasone †	0.6	1.5
Salmeterol	0.1	
Formoterol	0.024	
Tiotropium	0.018 (DPI) 0.005 (pMDI)	
Theophylline	400	
Aminophylline	600	
Montelukast	10	
Zafirlukast	40	

The total doses and strength of each medicine were adjusted using the DDD factor according to Equation 3.2. DDDs were calculated for all medicines in the analysis; for combination therapy inhalers, the DDD factor for the ICS component of the inhaler was utilised.

Equation 3.2:

$$\text{DDDs/1,000 people} = \frac{\frac{(\text{Number of inhalers} * \text{doses/inhaler} * \text{strength}) / (\text{DDD factor})}{30 \text{ days}}}{\text{Total population}} * 1{,}000$$

Lastly, the raw prescription volume in total items was also utilised, which takes into account neither the inhaler size nor the strength of the medication. Prescriptions where varying amounts of inhalers or different doses of inhalers were dispensed were treated equally and since no assumption of daily dosing was incorporated, no denominator for the month adjustment was needed as in the aPDD and DDD calculations (Equation 3.3).

Equation 3.3:

$$\text{Items/1,000 people} = \frac{\text{Items}}{\text{Total population}} * 1{,}000$$

All three metrics were population-standardised (per 1,000 people) using GROS mid-year population estimates for Scotland, available on a yearly basis, using the year prior to the receipt of medication (General Register Office for Scotland, 2013a). Each medication was accessed by its approved name, with the exception of grouping salbutamol and terbutaline (designated as 'SABA'), salmeterol and formoterol (LABA), aminophylline and theophylline (TP), and montelukast and zafirlukast (LTRA). Graphical plots of the time series data were clarified with correlation coefficients to assess similarity. Percentage change over the ten-year timespan was utilised to assess magnitude and trend for each of the three metrics. When there was evidence of interrupted or changing trends, percentage change was further broken down into smaller estimates, with ratios of these changes utilised to compare between metrics. The ratio of DDD to aPDD percentage change was used to estimate if the dose of a medication (as opposed to volume) was changing over time. For example, if the ratio was greater than 1.00 across the first five years, and then dropped below 1.00 for the next five years, it could be assumed that the average dose was higher in the beginning and subsequently levelled off. Of note, the DDD/aPDD ratio was only calculated in cases where the percentage change between the two metrics was drastically different overall.

Health board analysis

After data were assessed for Scotland as a whole to assess overall trend, a secondary analysis was conducted looking specifically at NHS Forth Valley with two comparator health boards, NHS Greater Glasgow & Clyde (GGC) and NHS Lothian, and comparing it to NHS Scotland in total. These comparator health boards were

chosen based on their vastly differing prevalence on the spectrum of respiratory disease, both from national data as well as data derived from the heat mapping analysis; it was hypothesised that the national average (from NHS Scotland) and NHS Forth Valley should lie between these two boards. Four composite medication groups were analysed, including short-acting inhalers (salbutamol, terbutaline and ipratropium), ICS (beclometasone, budesonide and fluticasone) combination therapy inhalers (fluticasone/salmeterol and budesonide/formoterol), and tiotropium. To standardise for the prevalence of respiratory disease in each health board and for Scotland as a whole, the estimated prevalence of asthma and COPD for each area was obtained from the QOF (Information Services Division Scotland, 2013b). These figures were available on a yearly basis from 2004 – 2012, although prior to 2006, patients could only appear on the asthma or COPD practice disease register and not both. An estimation of the number of people with respiratory disease in each area was determined by multiplying the summed prevalence of asthma/COPD with the population estimates for the area; from 2006 onward, the prevalence of COPD was conservatively reduced by 10% to account for diagnostic overlap in the sum of disease registers (Hardin *et al.*, 2011). Therefore, the resulting figures were population-standardised specifically to patients with respiratory disease rather than overall population (per 1,000 patients). Mood's median test was utilised to compare groups, with Tukey's test applied to distinguish inter-group differences.

3.3.2 Results

Scotland-wide analysis

For SABAs (salbutamol and terbutaline), utilisation increased overall by 23.0%, 28.2% and 26.8% for aPDDs, DDDs and items, respectively from 2003 – 2012 (Figure 3.6(a)). Use increased slowly from 2003 – 2007 (7.5 to 11.32% depending on metric), and then increased at a faster rate from 2008 – 2012 (28.0 to 29.6%). Estimates for aPDDs were approximately twice that of DDDs at all available time points. The use of ipratropium decreased overall by 67.8% for aPDDs, 70.8% for DDDs and 68.6% for items (Figure 3.6(b)). The largest decreases were seen from 2003 – 2007 (-48.2 to -52.4%), followed by a bump in utilisation during 2008; this reverted to the original decreasing trend thereafter, albeit at a slightly slower rate (-38.0 to -44.0%). Estimates for aPDDs and DDDs approximated each other relatively closely over time.

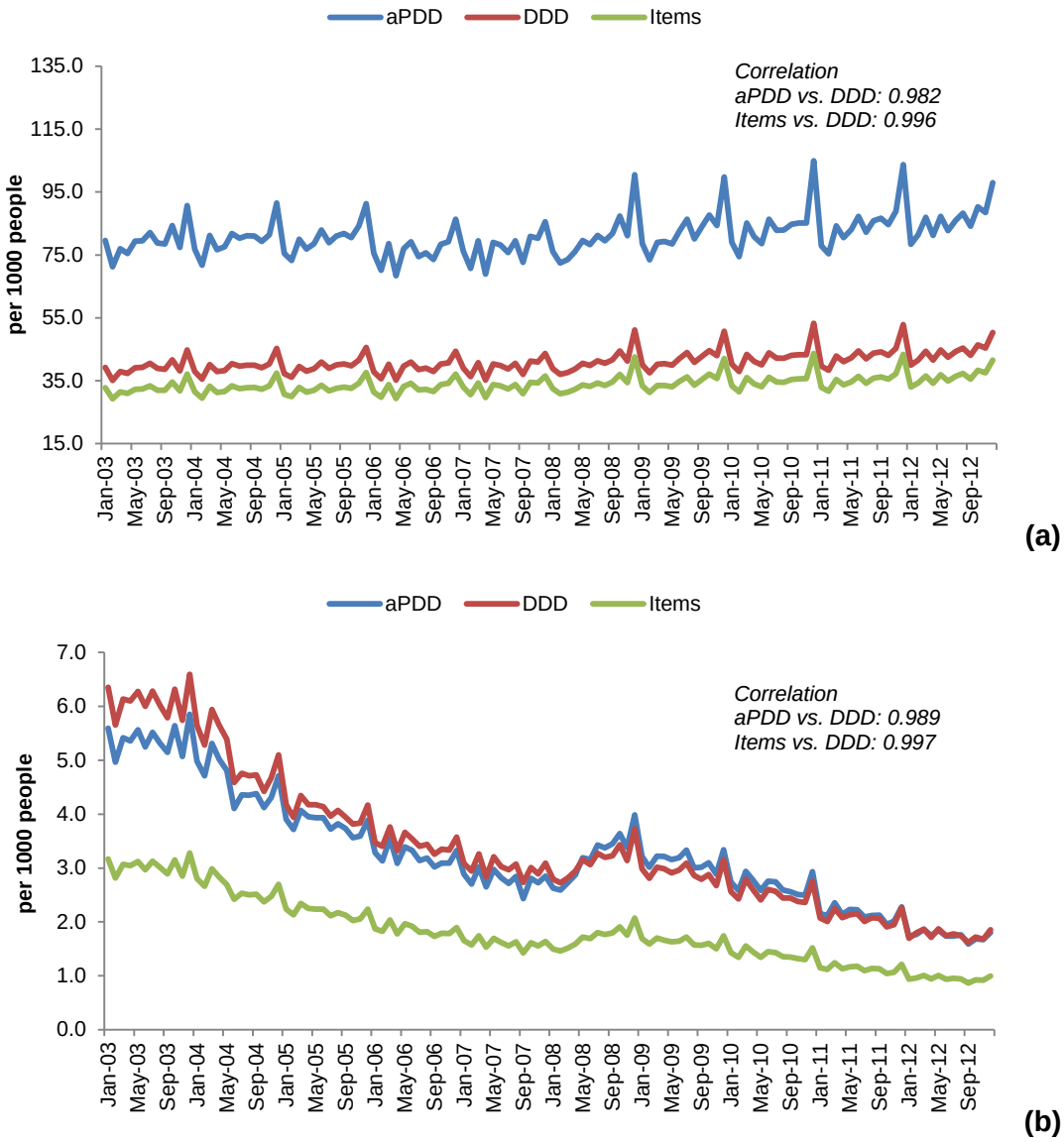
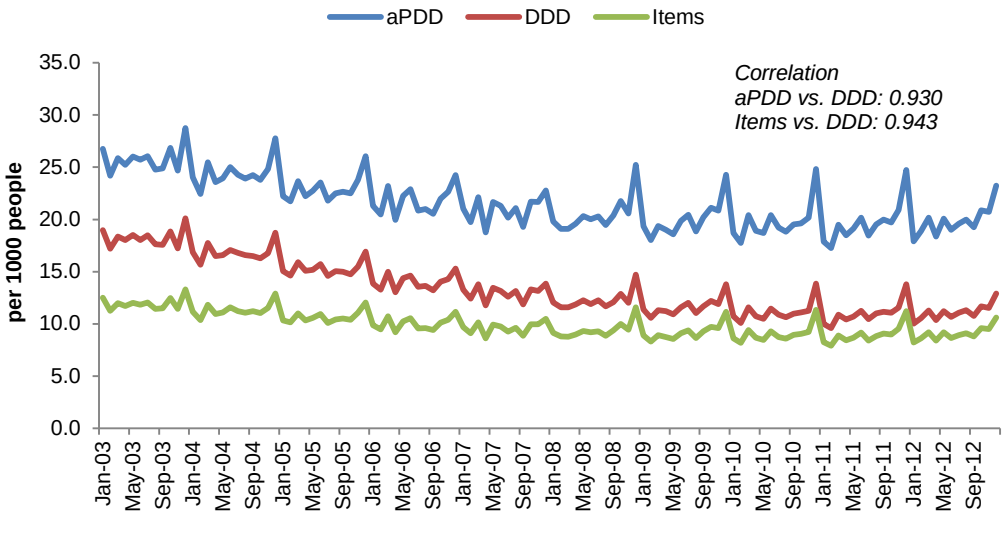


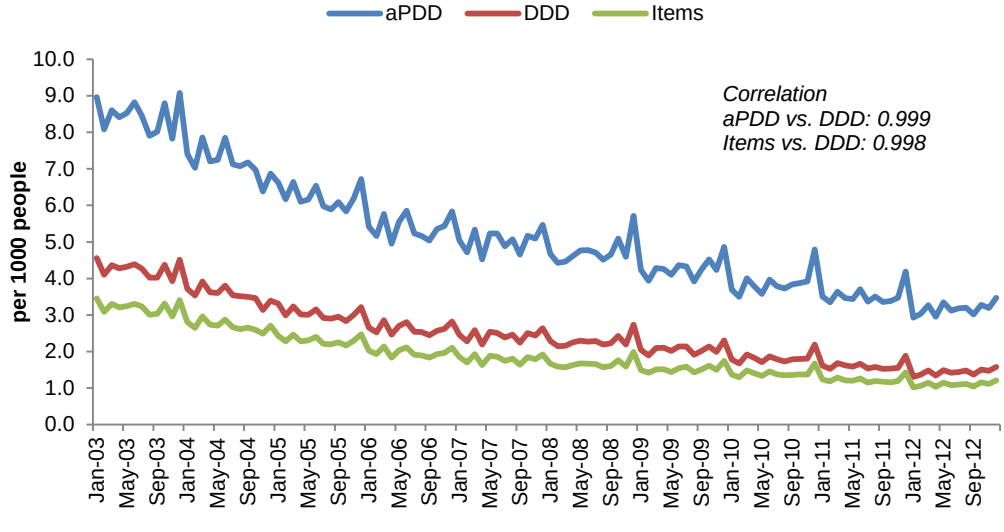
Figure 3.6: Medicine utilisation for short-acting inhalers in Scotland (2003 – 2012), for **(a)** SABAs and **(b)** ipratropium

Among ICS inhalers, beclometasone had the highest utilisation, with budesonide and fluticasone each at approximately one-third of beclometasone utilisation (Figures 3.7(a), (b) and (c)). All three ICS products decreased in utilisation. Overall beclometasone utilisation decreased 13.2% and 15.2% by aPDDs and items, respectively, but 32.5% by DDDs; decreases occurred from 2003 – 2007 (-14.8 to -27.1%), which levelled out and began increasing again from 2008 – 2012 (7.2 to 17.3%). The ratio of DDD/aPDD change was 1.82 for 2003 – 2007, changing to 0.41 from 2008 – 2012. Estimates for DDDs and items were approximately one-half of aPDDs. For budesonide, decreases in use were more dramatic, at 61.3%, 65.3%

and 64.8% for aPDDs, DDDs and items, respectively. Decreases were larger in magnitude from 2003 – 2007 (-39.0 to -44.4%) compared to 2008 – 2012 (-25.7 to -31.0%). Similar to beclometasone, utilisation as measured by aPDDs was greater than that by DDDs or items. Fluticasone utilisation also sustained large decreases, at 68.1% for aPDDs, 73.6% for DDDs and 69.3% for items. Again decreases were larger in 2003 – 2007 (-48.8 to -53.4%) compared to 2008 – 2012 (-28.2 to -35.7%). Unlike beclometasone and budesonide, estimates for aPDD and DDD were similar in magnitude, although with some divergence present prior to 2007.



(a)



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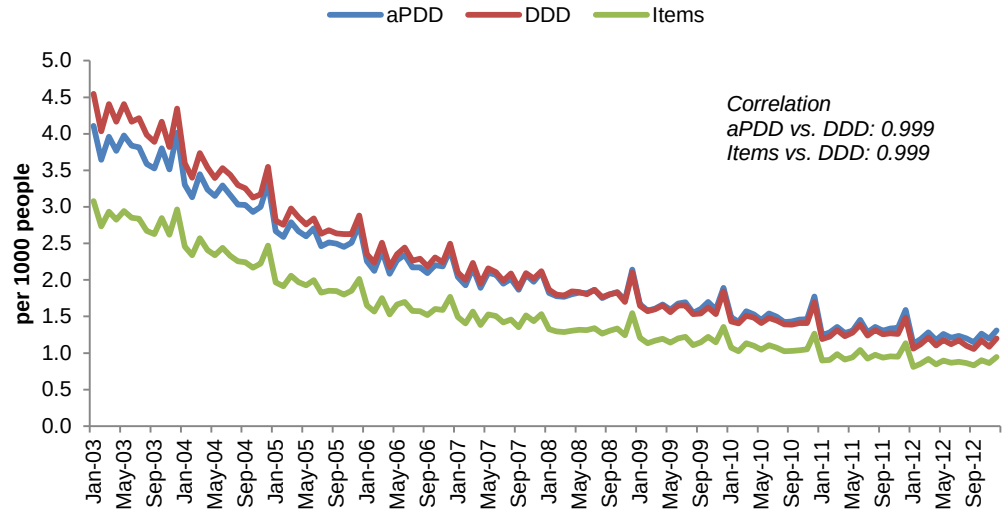


(c)

Figure 3.7: Medicine utilisation for ICS in Scotland (2003 – 2012) for **(a)** beclometasone, **(b)** budesonide and **(c)** fluticasone

LABA utilisation similarly decreased by a margin of 56.9% for aPDD, 56.9% for DDD and 60.7% for items (Figure 3.8). The trend was relatively consistent, albeit slowly levelling off in more recent years. LABA volume (by items) was approximately 20 to 30% of total ICS volume at any given time.

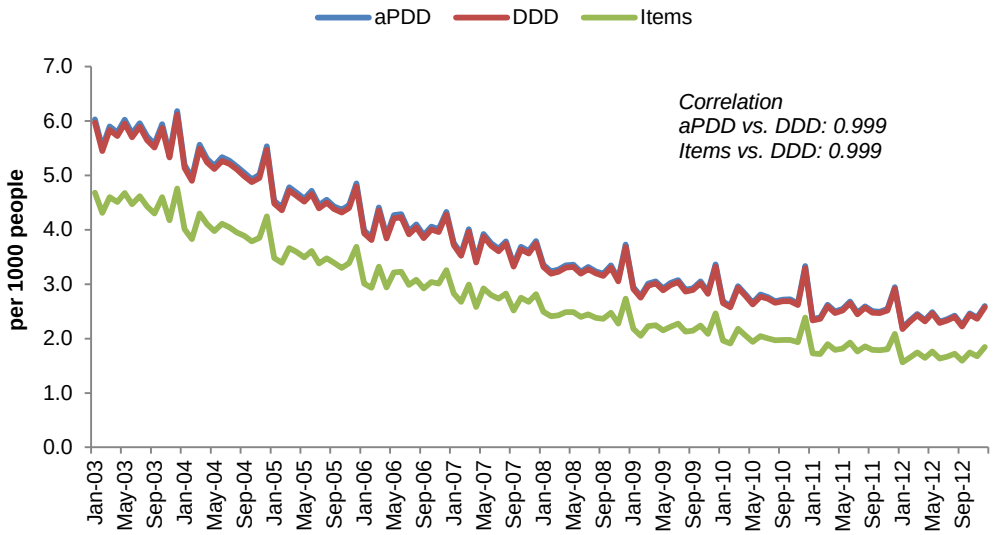
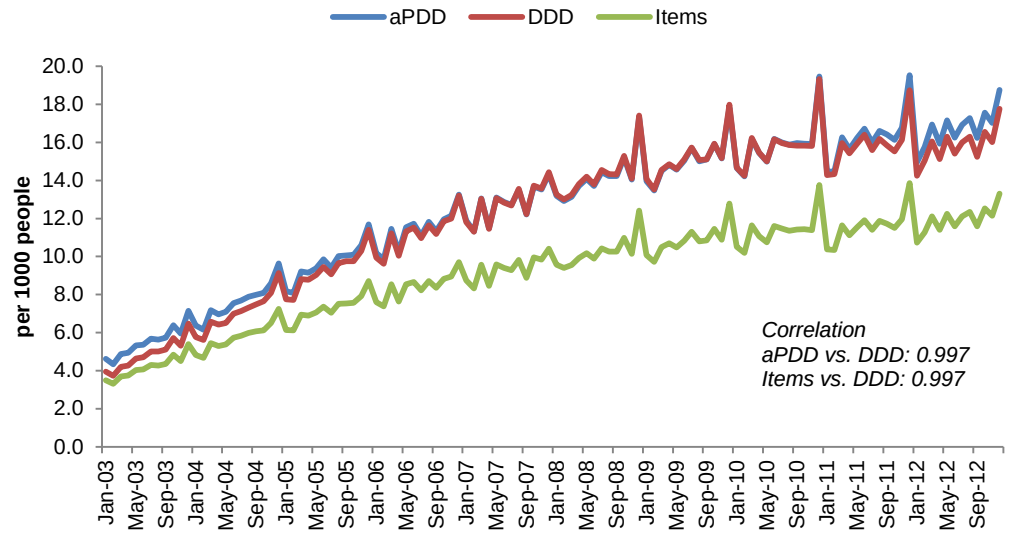
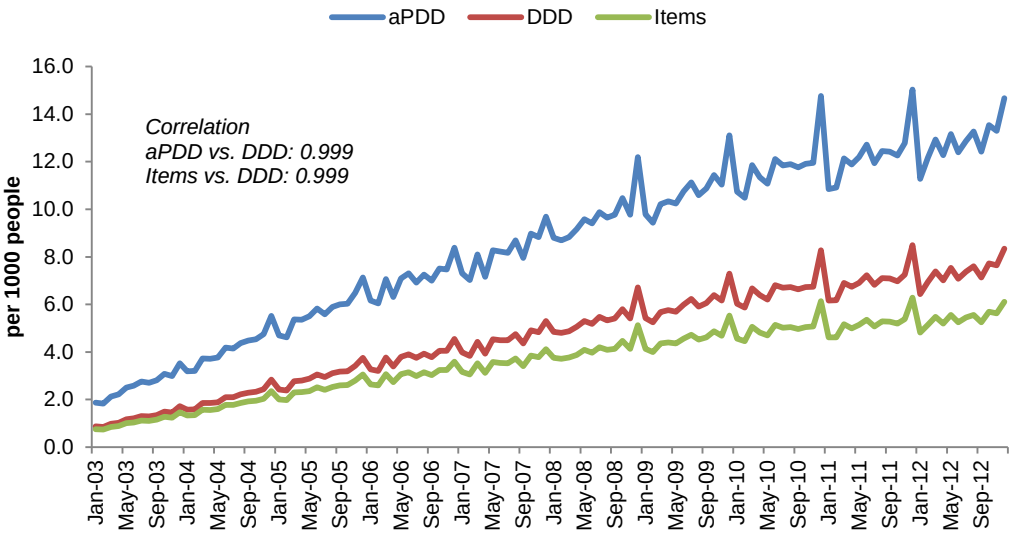


Figure 3.8: Medicine utilisation for LABA in Scotland (2003 – 2012)

Large increases in utilisation were seen for both combination inhalers fluticasone/salmeterol and budesonide/formoterol (Figure 3.9(a) and (b)). Overall utilisation was greatest for fluticasone/salmeterol and estimates for aPDDs and items were again similar (as with fluticasone). Utilisation increased 3.1-fold for aPDDs, 3.5-fold for DDDs and 2.8-fold for items; this was most evident from 2003 – 2007 (2.0 to 2.7-fold) compared to 2008 – 2012 (34.1 to 42.2%). The ratio of DDD/aPDD change was highest from 2003 – 2007 at 1.27, changing to 0.81 for 2008 – 2012. Although utilised less, budesonide/formoterol had larger growth over time, at 6.8-fold for aPDDs, 8.6-fold for DDDs and 7.1-fold for items. Increases were primarily in 2003 – 2007 (4.2 to 5.1-fold), slowing down in 2008 – 2012 (62.7 to 72.2%). The ratio of DDD/aPDD change held relatively stable over time, at 1.22 for 2003 – 2007 and 1.09 for 2008 – 2012. Similar to their root ICS products, estimates for aPDDs mirrored that of items for fluticasone/salmeterol but were greater for budesonide/formoterol.



(a)



(b)

Figure 3.9: Medicine utilisation for combination therapy inhalers in Scotland (2003 – 2012) for **(a)** fluticasone/salmeterol and **(b)** budesonide/formoterol

Tiotropium was licensed in the UK in 2002 and introduced into practice shortly after the timeframe of the analysis and use increased dramatically over the entire ten-year timespan, and particularly from 2003 – 2007 (Figure 3.10). Growth in aPDDs was higher in magnitude than DDDs, particularly from 2008 onward when the utilisation curves diverged.

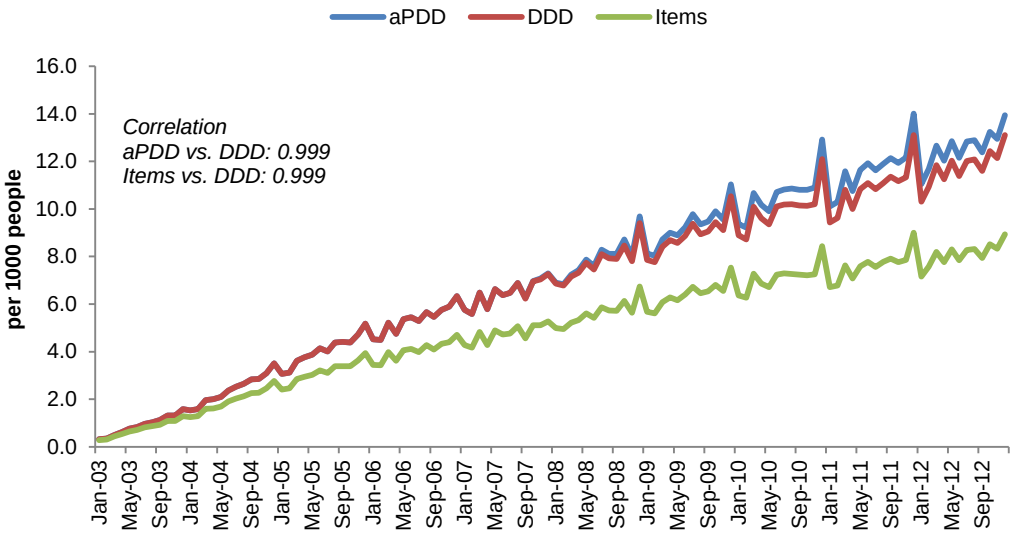


Figure 3.10: Medicine utilisation for tiotropium in Scotland (2003 – 2012)

Among the oral medications, use of theophylline decreased slowly over time by 19.4% for DDDs and 26.3% for items (Figure 3.11). Decreases were evident from 2003 – 2007 (-17.0 to -23.3%), which stabilised and increased thereafter (4.6 to 7.5%). LTRA utilisation (montelukast and zafirlukast) increased 2.1-fold for DDDs and 1.7-fold for items (Figure 3.12); these increases were relatively stable over time (62.7 to 94.5%).

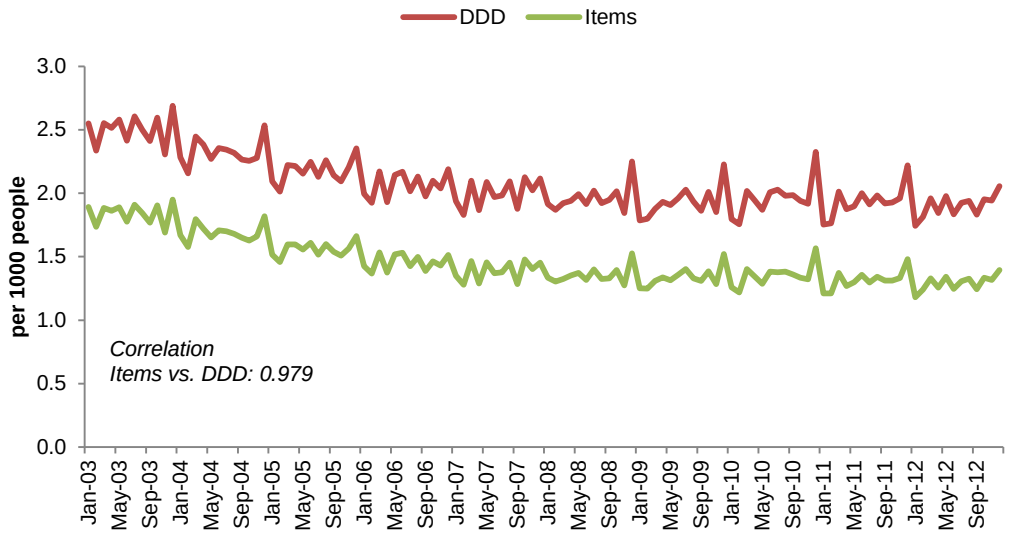


Figure 3.11: Medicine utilisation for theophylline in Scotland (2003 – 2012)

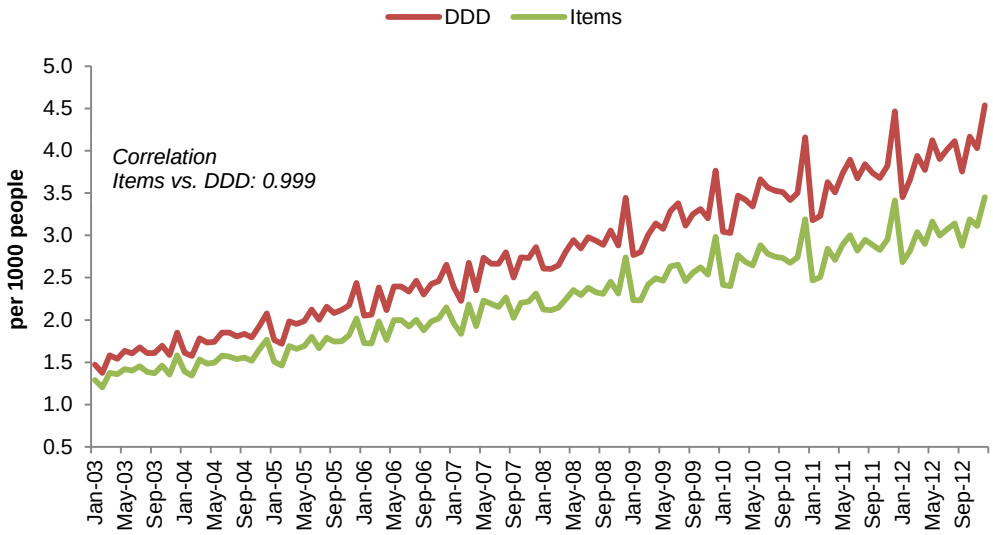


Figure 3.12: Medicine utilisation for LTRA in Scotland (2003 – 2012)

Health board analysis

In the health board analysis (Figures 3.13(a), (b), (c) and (d)), median utilisation for short-acting inhalers was highest for NHS Greater Glasgow & Clyde (522 items/1,000 patients) and lowest for NHS Lothian (405 items/1,000 patients), with estimates for NHS Forth Valley and NHS Scotland both placed in the middle at 471 and 480 items/1,000 patients, respectively (overall test $p<0.001$). For both ICS and combination therapy inhalers, median utilisation was similar for NHS Greater Glasgow and Clyde, NHS Forth Valley and NHS Scotland, ranging 166 to 188 items/1,000 patients for ICS and 191 to 201 items/1,000 patients for combination therapy inhalers. However, for both therapeutic classes, utilisation was significantly lower in NHS Lothian at 132 and 162 items/1,000 patients, respectively ($p<0.001$). Lastly, for tiotropium, utilisation was similar between NHS Greater Glasgow & Clyde and NHS Forth Valley at 99 and 94 items/1,000 patients, respectively but was significantly lower for both NHS Scotland (74 items/1,000 patients) and NHS Lothian (51 items/1,000 patients) ($p<0.001$). There was a crossover of trends between NHS Greater Glasgow & Clyde and NHS Forth Valley, with utilisation in NHS Forth Valley having a larger decrease for ICS and a smaller increase for tiotropium.

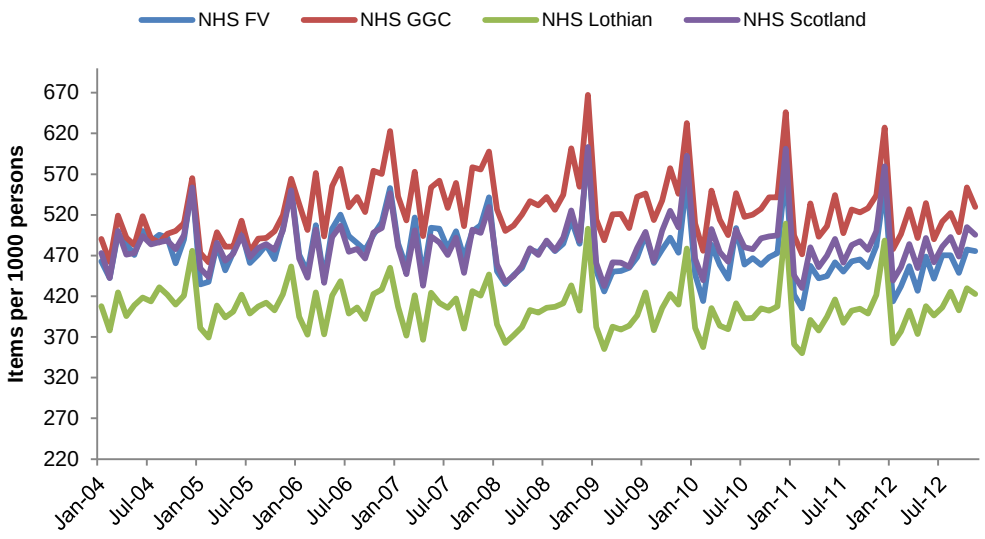


Figure 3.13a Items/1,000 patients with respiratory disease in NHS Forth Valley, NHS Greater Glasgow & Clyde, NHS Lothian and NHS Scotland (2004 – 2012) for short-acting inhalers

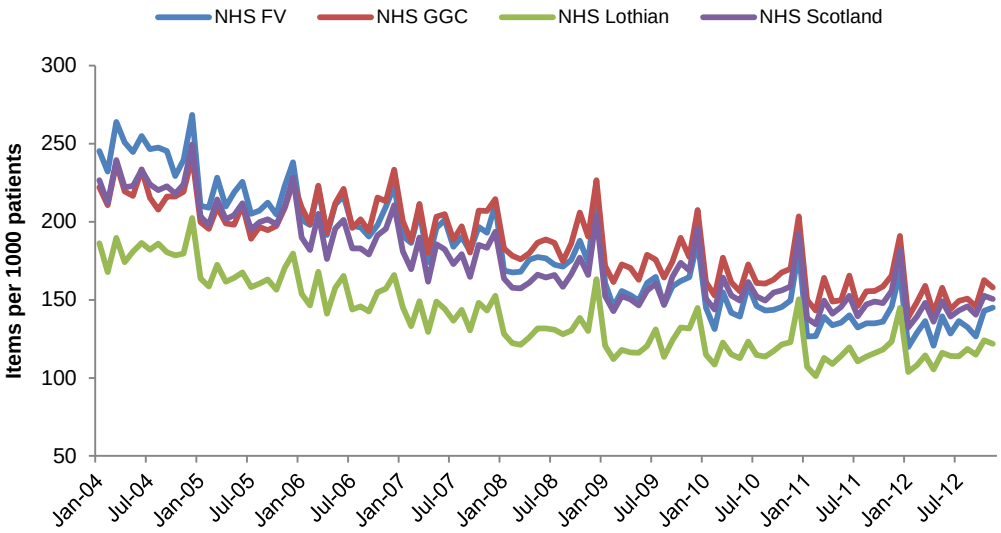


Figure 3.13b Items/1,000 patients with respiratory disease in NHS Forth Valley, NHS Greater Glasgow & Clyde, NHS Lothian and NHS Scotland (2004 – 2012) for ICS

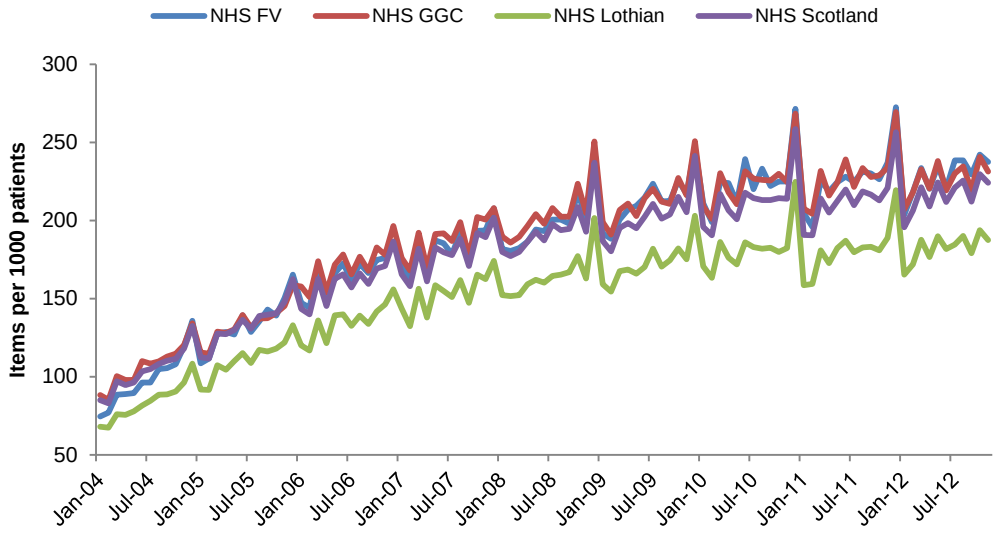
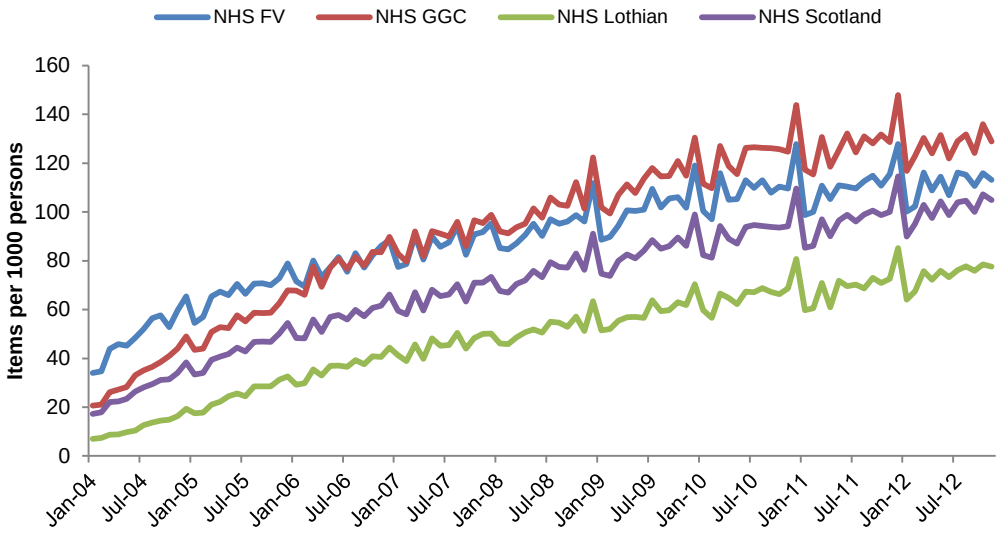


Figure 3.13c Items/1,000 patients with respiratory disease in NHS Forth Valley, NHS Greater Glasgow & Clyde, NHS Lothian and NHS Scotland (2004 – 2012) for combination therapy inhalers



(d)

Figure 3.13d Items/1,000 patients with respiratory disease in NHS Forth Valley, NHS Greater Glasgow & Clyde, NHS Lothian and NHS Scotland (2004 – 2012) for tiotropium

3.3.3 Discussion

Trends over the ten years show that the utilisation of combination inhalers, tiotropium and LTRAs has increased while use of single-agent ICS and LABA inhalers has decreased.

Medicine utilisation can be measured in a variety of ways and each method has its own strengths and limitations. The present analysis compared three different methods to assess the prescribing of respiratory medicine in Scotland. Item counts are an easy metric to obtain and analyse but because no weight is given to dose or inhaler size/quantity, every prescription is treated equally, even when their characteristics (the number of inhalers dispensed, etc.) may dictate otherwise. Of the three methods utilised, DDDs are the most widely known and internationally recognised medicine utilisation metric as endorsed and defined by the WHO. However, as DDDs include consideration of the strength of the medication, the measure is also a representation of consumption, and will trend with changes in strength as much as changes in quantity. aPDDs, although less frequently utilised in the literature, disregard the dose/strength characteristics of the medication and instead evaluate utilisation based on an assumption of normal daily dosing. Accordingly, comparison of DDDs and aPDDs can provide an assessment of the change in average dose of the medication over time.

DDD estimates for beclometasone decreased at a steeper rate than corresponding aPDD estimates. Similarly, DDD estimates increased at a steeper rate than aPDDs for fluticasone/salmeterol and budesonide/formoterol. This indicates that the relative dose/strength of beclometasone has decreased over time, and that the dose of combination therapy inhalers has increased over time. Using the latter case as an example, two scenarios are possible: either the dose that patients are prescribed has increased or the strength of the inhalers dispensed has increased (while maintaining the same dose for the patient). For instance, a gradual shift from an average of beclometasone 100 micrograms daily to beclometasone 200 micrograms daily over time (keeping a stable item count) would lead to an increase in DDDs but a stable trend for aPDDs. It is feasible that patients might be receiving the same daily dose and using twice the number of puffs from the lower dose inhaler but this would half the supply that the inhaler provides and should be balanced by an

increase in *Paid Quantity*. The more likely scenario is that the daily dose that patients are receiving has increased over time although without the prescription instructions it would be impossible to verify.

An increase in the average dose of combination therapy inhalers may be the result of these medications gaining an indication for the treatment of COPD after their initial approval for the treatment of asthma. Seretide Accuhaler® and Symbicort Turbohaler® were accepted for use for patients with COPD within NHS Scotland by the Scottish Medicines Consortium (SMC) in 2003 and 2004, respectively – several years after their market approvals for patients with asthma (Scottish Medicines Consortium, 2008). Although the timeframe of the data does not allow for a good control comparator which would require data prior to the secondary indication approval, the recommended doses for COPD are 500 micrograms twice daily for fluticasone/salmeterol and 400 micrograms twice daily for budesonide/formoterol (both doses would be high-dose therapy for patients with asthma) and increased use of these therapies for this indication would plausibly increase the average dose over time. This correlates with the largest increases in DDDs vs. aPDDs, which were seen in the first five years of the analysis, from 2003 – 2008. A lack of diagnostic data associated with the PIS database limits further supposition.

Comparison of estimates between aPDDs and DDDs also requires close consideration of how the medication is supplied by the manufacturer. Fluticasone-containing products, both single agent and combination are designed to supply 30 days of medication, with 60-dose inhalers for DPI formulations and 120-dose inhalers for pMDI formulations. For these medications, aPDDs and DDDs provide an approximate estimation of each other. However, for beclometasone and budesonide-containing products, 100-dose and 200-dose inhalers are utilised which result in variations between 25 and 100 day supplies of medication and increase the aPDD estimate over the DDD estimate when considered at a stable dose/strength trend over time. Estimates for DDDs also take the size of the inhaler into account, but are based upon a DDD factor which functions as a standardised unit of measurement and may not reflect the recommended or average daily dose for the medication (World Health Organization, 2013b). This is particularly the case with situations that vary from the norm such as: differing patient characteristics for example in children, who would require lower doses and therefore are

overestimated by DDDs; medications with different formulations such as the potency differences between beclometasone formulations Clenil Modulite® and Qvar®; and combination therapies, where the DDD factor of one component may not mirror the other. The good approximation of aPDDs/DDDs with each other, for the 30-day dosage formulations, demonstrate that among a large population, the DDD factor does approach the average daily dose.

This analysis, beyond the clinical implications present within the data, also allowed for exploration of different types of medicine utilisation metrics to inform future research methodology. Item counts are a crude and unadjusted metric and are not the most optimal measure; however, these data may be the only limited data available to some clinicians/researchers. More detailed data allows a researcher to calculate the aPDD or DDD, which do approximate each other under certain dosage form conditions and for medicines where the dose is not dramatically changing over time. However, based on this analysis, DDDs should emerge as the preferred metric, based on its international recognition and utility across a variety of formulations.

Most medications had relatively stable utilisation trends, whether increasing or decreasing. However, ipratropium was subject to an unusual increase in utilisation throughout 2008, distinct from its otherwise decreasing trend. The decreases in utilisation are likely to have been influenced by product introduction and emerging clinical data at the time. Tiotropium was first licensed in the UK in 2002 and many patients were likely switched from ipratropium to its longer-acting counterpart in the years after based on the improved dosing regimen and efficacy. Additionally, two large studies looking at cardiovascular events and mortality associated with ipratropium were published during the latter half of 2008 and both indicated an unfavourable risk profile for the medication and -00pan increased risk of adverse events (Lee *et al.*, 2008; Singh *et al.*, 2008). Although the second study also included tiotropium in the analysis, only ipratropium was consistently associated with an increase in major adverse cardiovascular outcomes. These two factors are likely to have contributed to the decreasing utilisation of ipratropium over time but fail to account for the unusual bump in utilisation during 2008. No corresponding changes in other short-acting inhalers (salbutamol or terbutaline) or tiotropium matched this trend.

Utilisation patterns exhibited seasonal variation across all medications, with consistent increases seen during the months of November and December each year. This effect could be the result of seasonal changes increasing the risk for disease exacerbations. Asthma has a distinct seasonal timeline particularly for children, who experience an increase in medical visits and hospitalisations in the autumn – an effect that has been hypothesised to be the result of viral infections incurred from the start of the school year (Julious *et al.*, 2011; Osborne *et al.*, 1996). Seasonal changes in asthma symptoms have a less clear pattern for adults but generally peak in the spring as a result of an increased outdoor allergen burden (Osborne *et al.*, 1996). For COPD, exacerbations are more frequent in the colder winter months when host defences are diminished and respiratory infections are more common (Donaldson *et al.*, 2012; Jenkins *et al.*, 2012; Rabe *et al.*, 2013). Accordingly, changes in medication utilisation throughout different times of the year would be anticipated, primarily for short-acting rescue therapies. However, in the current analysis, dispensing of both rescue and maintenance therapies increased during November/December, which may be the result of GP practices closing for periods during the holiday season and ensuring that patients have adequate supplies of their medication during this time rather than seasonality exerting an effect on exacerbations.

Utilisation of all single-agent ICS inhalers decreased over the ten years, while the use of combination inhalers increased dramatically. Although single-agent LABA inhalers have been available on the UK market since 1991, the first combination inhaler Seretide® (fluticasone/salmeterol) was not approved for asthma until 1999 or for COPD until 2002. Versions of the BTS/SIGN guideline published before 2003 advocated a gradual increase in ICS doses before addition of a LABA to therapy, reserving combination therapy primarily for steps 4 and 5 or for patients who were intolerant to higher doses of ICS at step 3 (British Thoracic Society, 1997). After the publication of the landmark studies by Greening *et al*. (1994) and Woolcock *et al*. (1996), evidence began to mount regarding the relative benefits of combination therapy over increased doses of ICS. Subsequently, in the first joint asthma guideline published by BTS/SIGN in 2003, combination therapy became a first-line recommendation for step 3 therapy albeit over a wide dose range (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2003). This change has

likely resulted in combination inhalers being considered earlier in asthma step therapy, and single-agent ICS inhalers being utilised less frequently in more advanced steps.

An increase in the use of combination inhalers may also reflect an overall worsening of respiratory disease across Scotland, particularly as it was accompanied by an increase in rescue therapy (salbutamol and terbutaline). Worsening of respiratory disease may result either in actuality or artificially due to increased awareness of the disease by patients and healthcare professionals. Estimates from the QOF show that the prevalence of asthma increased from 5.4% in 2004/05 to 6.0% in 2011/12 and the prevalence of COPD has increased in magnitude from 1.8% in 2004/05 to 2.0% in 2010/11 – the register was redefined in 2011/12, skewing historical comparison with this year (Information Services Division Scotland, 2013b). Under QOF rules prior to 2006/07, patients could not be listed concurrently on both the asthma and COPD practice registers thus requiring caution with interpretation of prevalence estimates during this time.

The QOF scheme includes a variety of quality indicators pertaining to the diagnosis and care of asthma and COPD (Table 3.2). These indicators have been updated periodically since the introduction of the scheme based on evolving clinical practice but have consistently included indicators relating to appropriate diagnosis and follow-up for patients with respiratory disease. With these aspects of care formalised into an incentivised programme, disease awareness among clinicians could increase, leading to an increase in medication utilisation, either through identifying new cases or better managing existing patients.

Table 3.2: QOF indicators in the asthma and COPD clinical domains (2012/13)
** indicators are under a separate clinical domain for smoking, but include patients diagnosed with asthma and/or COPD*

Asthma	**COPD**
Produce a practice register	Produce a practice register
Diagnosis confirmed by spirometry or peak flow	Diagnosis confirmed by post-bronchodilator spirometry
Smoking status recorded for adolescents in the last 15 months	FEV_1 recorded in the last 15 months
Patients with measures of reversibility recorded	Patients given an influenza immunisation
Asthma review for each patient in the previous 15 months	COPD review with MRC dyspnoea score for each patient in the previous 15 months
Smoking status recorded for adults in the last 15 months *	
Smoking cessation advice/referral offered in the last 15 months to adults who currently smoke *	

There is a lack of good data regarding how the QOF scheme has affected clinical care within the UK. Commentary in the literature has questioned the ethics and success behind 'pay-for-performance' models such as QOF (Hutchison, 2008; Woolhandler *et al.*, 2012). Campbell *et al*. (2007) assessed the quality of care within clinical domains for a sample of GP practices in 1998 (before introduction of the QOF) and further in 2003 and 2005 (after introduction of the QOF). Changes in clinical quality scores pre- and post-QOF introduction were variable according to the chronic disease assessed: improvements that were seen were modest in nature and lacked correlation with indicators which were financially incentivised (Campbell *et al.*, 2007). A follow-up of these GP practices showed that by 2007, improvements in care had stalled once targets has been achieved and the quality of care for conditions that were not linked to incentives had declined (Campbell *et al.*, 2009). A later systematic review evaluating the broader impacts of the QOF also found improvements in clinical care to be varied and limited in scope and effects on cost, professional behaviour and patient experience to be inconsistent (Gillam *et al.*, 2012). The evidence behind general financial incentives other than the QOF is lacking. A Cochrane review of seven studies evaluating the impact of financial incentives for primary care performance found insufficient evidence to provide a clear recommendation (Scott *et al.*, 2011).

Whether the QOF has had a discernible effect on clinical care in the UK or specifically on the treatment of asthma and/or COPD seen in this analysis is unclear. The current analysis included prescription data starting in 2002 and no significant changes in trend after 2004 (the first year of the QOF) were seen. However, as noted by Campbell *et al*. (2009), it is reasonable to assume that GPs were aware of future changes arising within the GMS contract and may have changed their practices prior to 2004. Despite its voluntary nature, approximately 99% of GP practices in Scotland have participated in the QOF since its inception, and therefore a control comparator against the 'QOF intervention' is lacking (Information Services Division Scotland, 2010b).

For the health board analysis, a modification of QOF-derived disease prevalence was used to standardise for differences in dispensing between health boards. A 10% overlap between asthma and COPD diagnoses was assumed based on estimates available in the literature, but these estimates are known to vary based on definition and may be even higher (Hardin *et al.*, 2011; Soriano *et al.*, 2003). While the estimation of the degree of overlap may have altered the number of people estimated to have respiratory disease within each health board and the resultant dispensing rate, it will not have disrupted the comparison among the boards.

The comparison with NHS Greater Glasgow & Clyde and NHS Lothian Health Boards provides an estimate of the relative treatment burden in NHS Forth Valley and further compares it to broader estimates for NHS Scotland as a whole. Intensity mapping had revealed areas surrounding Glasgow and Edinburgh to be at opposing ends of the prevalence spectrum for both asthma and COPD and these boards were used to benchmark dispensing rates for NHS Forth Valley. The shape of dispensing trends for maintenance therapies was similar among the three boards but the population-adjusted dispensing rates for NHS Forth Valley more closely resembled that of NHS Greater Glasgow & Clyde. This may reflect that patients in NHS Forth Valley and NHS Greater Glasgow & Clyde have more advanced disease requiring more treatment or that treatment is simply more aggressive in these areas. Notably, the dispensing rates for short-acting inhalers in NHS Forth Valley were significantly less than NHS Greater Glasgow & Clyde. Coupled with similar rates of maintenance therapy dispensing, this may indicate a comparatively better degree of symptom

control in NHS Forth Valley. NHS Lothian, with lower rates of dispensing for both as-needed and maintenance therapies, may have patients with milder disease overall. Overall, NHS Forth Valley was largely similar to NHS Scotland, indicating that the health board provides a useful and externally valid population to study for respiratory disease within Scotland.

Local health governance may also play a role in medication utilisation through the influence of MCNs. In 1998, the concept of MCNs was launched in NHS Scotland as an effort to improve the quality of care for patients with chronic medical conditions. MCNs form a virtual network of clinicians focused on working to improve patient-centred care for a particular clinical problem (Scottish Executive, 1999). Each MCN is meant to be unique and able to develop its own framework but is guided by a set of core principles, which include formulation of a management structure, use of a multidisciplinary approach, formulation of quality assurance measures and exploration of 'value for money', among others (Scottish Executive, 2002). There are several MCNs with a focus in respiratory disease across Scotland, including the NHS Forth Valley Airways MCN. These groups, who were first formalised during the time frame of the present analysis, are likely to contribute to differences in medication utilisation seen among health boards.

3.4 Conclusions

The burden of respiratory disease in Scotland is geographically-dependent, with a relatively concentrated prevalence, particularly of COPD, in the central belt. Medication utilisation trends indicate a shift towards combination inhaler therapy over the decade, although whether this is related to changes in disease severity cannot be established in this analysis. Overall, across the 14 health boards in NHS Scotland, NHS Forth Valley was ranked 7th and 4th for overall prevalence of asthma and COPD, respectively. Medication utilisation within the board suggested the population to be a suitable and externally valid reference population for respiratory disease in Scotland as a whole.

Chapter 4:

Asthma

4.1 Introduction, aims and objectives

Using regional-level data from the FV and KY databases, data were examined separately by diagnosis beginning with patients with asthma. Patients were first described as a function of their demographic characteristics, followed by a survey of overall medicine utilisation trends. Lastly, analyses were undertaken with regard to treatment patterns specific to asthma, with an added external questionnaire of clinicians within the NHS Forth Valley Health Board. When possible, results were compared between the FV and KY databases to provide context and discussion. The objectives were to:

- Compare the demographics of the two populations of patients with asthma;
- Describe medicine utilisation in terms of general trends and with categorisation into steps of the BTS/SIGN guideline;
- Quantify levels of adherence and persistence with respiratory medicines;
- Evaluate therapy transitions on initiation of combination therapy;
- Assess clinician understanding of prescribing for asthma according to the BTS/SIGN guideline in NHS Forth Valley;
- Identify areas for quality improvement in the clinical care of asthma in NHS Forth Valley and Kentucky.

4.2 Demographics

4.2.1 Methods

Using the FV and KY databases, data were analysed for the three-year period from January 2007 – December 2009. The patient population with asthma for a given year was defined as the patients within each respective database who had a physician diagnosis of asthma (inclusion on the disease register [FV database] or qualifying ICD9-CM code [KY database]) and received a prescription relating to the care of their asthma during that year. This population was cross-referenced with the patient population with physician-diagnosed COPD to estimate the percentage of patients with a co-morbid diagnosis. Age distributions were constructed using 10-year age bands with a terminal category of greater than or equal to 70 years of age, and then analysed separately according to sex (queries 4 – 5). This distribution was supplemented with a 2008 age/sex prevalence distribution for the FV database

adjusted with mid-year population estimates for NHS Forth Valley (General Register Office for Scotland, 2013a). In October 2008, there were 57 practices in NHS Forth Valley with an average practice list size of 5,390 patients (Information Services Division Scotland, 2010a). As the FV database only collected patient data from 46 practices, an 80% adjustment factor was applied to the prevalence estimates to compensate for the partial population capture. As the KY database was obtained from a single third-party healthcare provider and lacked base population figures, geographic prevalence estimates were unable to be made with available data.

As the FV database was derived from the EHR, further detailed information on smoking status and deprivation was also available; no comparable data were available within the KY database. Smoking status was categorised into three groups: never smokers, current smokers, and former smokers. Each smoking status was accompanied by a date on which it was assessed and a limited number of patients had multiple statuses recorded within the three-year analysis window. Deprivation was assessed using the Scottish Index of Multiple Deprivation (SIMD) 2009 score, which ranks small areas (data zone boundaries utilised in the heat mapping analysis) of Scotland according to 7 weighted domains of socioeconomic determinants (The Scottish Government, 2012c). As the FV database contained no specific patient identifiers, GP postcode was used as a surrogate for assessing neighbourhood deprivation. Each postcode was matched to a SIMD data zone, and based on the area score, patients were categorised into quintiles, ranging from ‘most deprived’ to ‘most affluent’. Both smoking status and deprivation were assessed independently and then further stratified by age and sex. Differences in age, sex, smoking status and deprivation distributions were assessed using a 2-proportion test and a Bonferroni correction to adjust for bias imposed by multiple comparisons.

4.2.2 Results

4.2.2.1 Age, sex and prevalence

A total of 16,664 distinct patients with asthma receiving treatment were identified within the FV database from 2007 – 2009; the best populated year of data was 2008 with 14,092 patients. Nine hundred and twenty patients (5.5%) were recorded as having comorbid COPD. The proportion of women with asthma (56.2%) was greater

than men and median age for women (40 years [IQR: 23 to 57 years]) was greater than men (35 years [IQR: 16 to 52 years]; p<0.001). The age distribution of the population was diverse, and distinct according to sex (Figure 4.1). For men, a bimodal distribution was evident, with the highest percentage of male patients aged 10 to 19 years old and 40 to 49 years old at 17.5% and 15.0%, respectively. For women, the percentage of patients increased gradually to a peak of 16.7% at 40 to 49 years old. The proportion of men was statistically significantly larger for patients less than 20 years of age, whereas the proportion of women was larger for patients greater than or equal to 40 years of age.

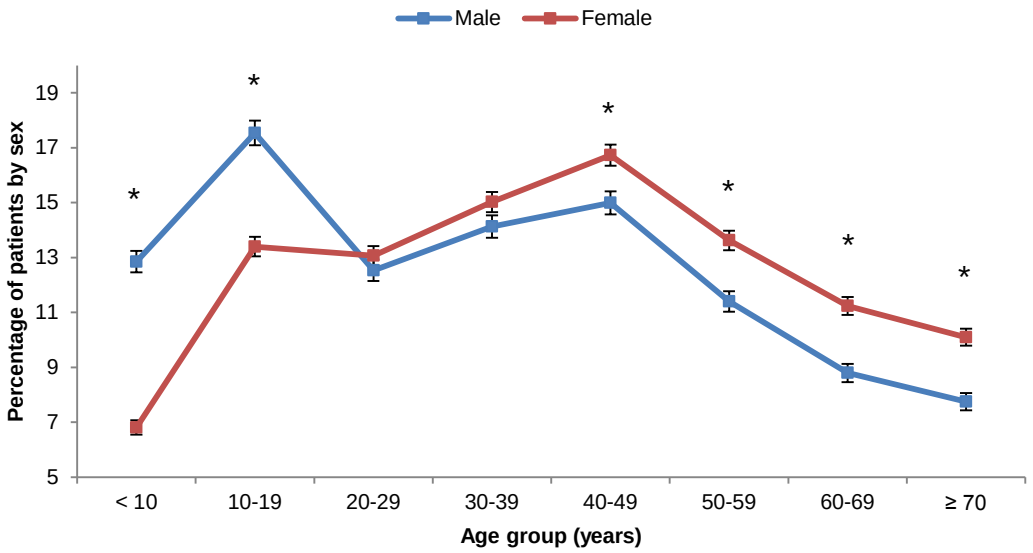


Figure 4.1: Age distribution of patients with asthma in the FV database by sex (2007 – 2009)
** p<0.05 for the difference between men and women*

Eight thousand eight hundred and thirty-three distinct patients were identified within the KY database during 2007 – 2009, with 2008 the most populated year with 5,712 patients. A total of 1,110 patients (12.6%) were recorded with concurrent claims for chronic bronchitis, emphysema or COPD. Women constituted 57.0% of the total population, with a higher median age than men at 36 years (IQR: 18 to 49 years) compared to 22 years (IQR: 8 to 43 years) (p<0.001). A large proportion of men (46.0%) were less than 20 years of age, whereas female patients had a more even distribution, peaking at 40 to 49 years of age at 20.0% (Figure 4.2). Statistically significant differences in the sex distribution were noted for all age groups less than 60 years of age.

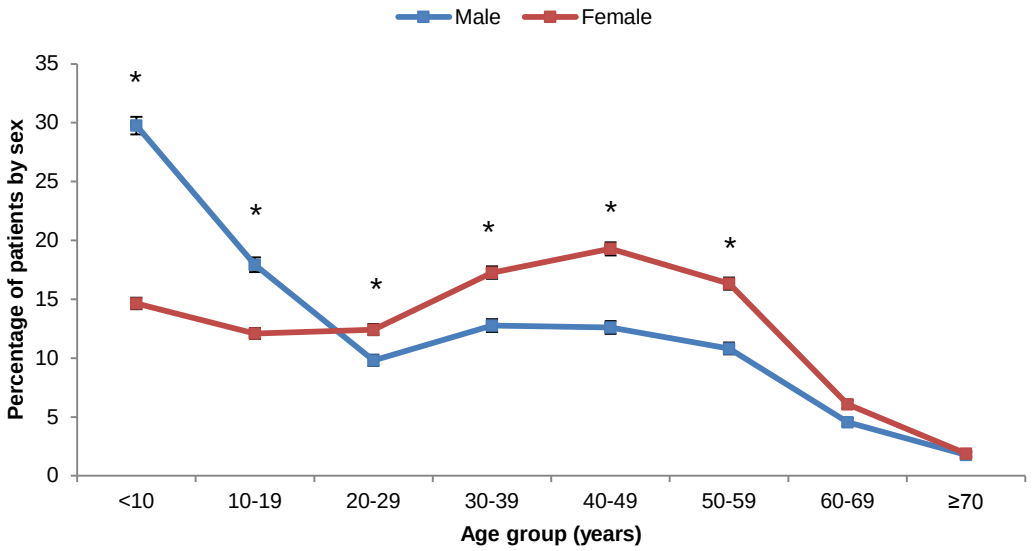


Figure 4.2: Age distribution of patients with asthma in the KY database by sex (2007 – 2009)
** p<0.05 for the difference between men and women*

Comparison of demographics between the FV and KY databases revealed a different distribution (Figure 4.3). As reflected in the median age within each database, male children under 10 years of age made up the largest proportion of patients with asthma in the KY database at 11.6% and in contrast adult females from 40 to 49 years of age were the most prevalent group with asthma in the FV database, at 9.9%. A total of 11.0% of patients in the FV database were aged 70 years old or greater compared to 2.7% in the KY database.

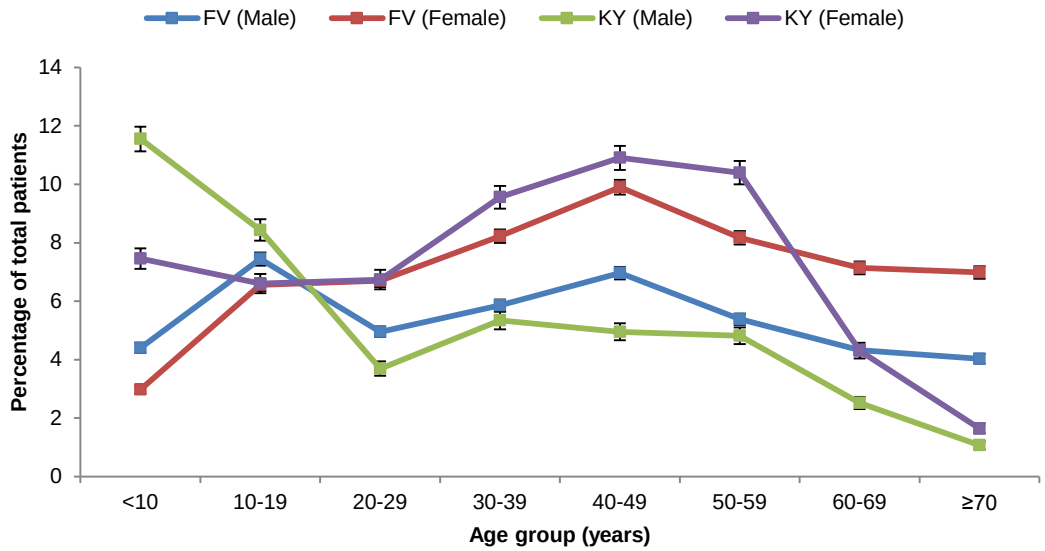


Figure 4.3: Comparison of age/sex distributions of patients with asthma in the FV and KY databases (2007 – 2009)

When standardised to adjusted population estimates for NHS Forth Valley in 2008, the overall prevalence of asthma was different between the sexes, at 5.5% and 6.7% for men and women, respectively (p<0.001). For men, peak prevalence (6.8%) was reached at 10 to 19 years of age and remained stable thereafter at 5.0 to 5.8% (Figure 4.4). For women after adolescence, prevalence was relatively flat ranging from 6.4 to 7.5%, with a peak occurring at age 60 to 69 years. The prevalence rate was higher for male patients in adolescence, evening out during teenage years, and then becoming higher for women for the remainder of adulthood.

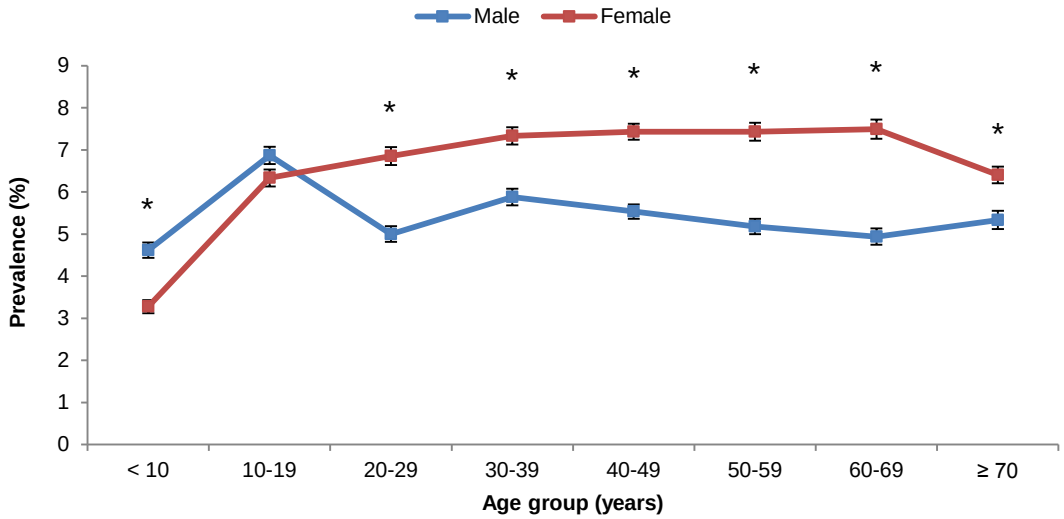


Figure 4.4: Prevalence of asthma in the FV database by age and sex (2008)
** p<0.05 for the difference between men and women*

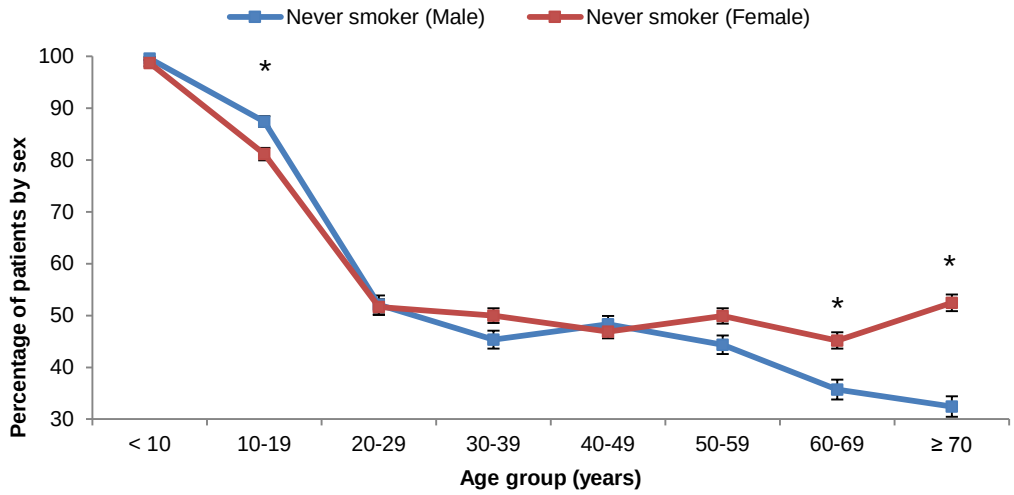
4.2.2.2 Smoking status

Smoking status data were available at some point for 14,248 (85.5%) patients in the FV database during 2007 – 2009. The number of patients with a smoking status recorded in a given year was variable, ranging from 43.7 to 59.5%, with 2008 best populated (Table 4.1). The slight majority (55.3%) of patients classified across all three years were classified as never smokers, with the remainder of patients split between current smokers (19.5%) and former smokers (20.6%). A small number of patients (4.6%) had multiple smoking statuses recorded during the three years assessed. No differences were noted in the distribution of smoking statuses for the individual years assessed.

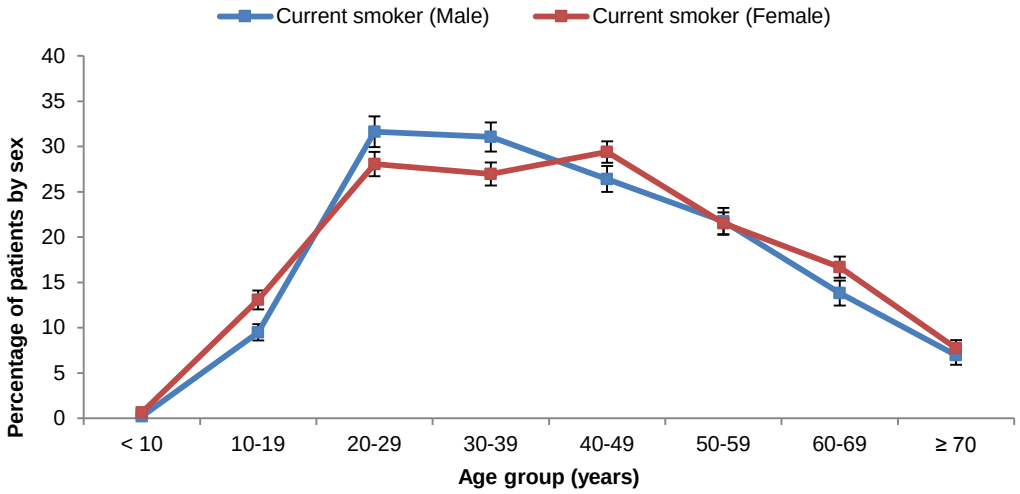
Table 4.1: Smoking status of patients with asthma in FV database (2007 – 2009)

Smoking status	n (%)		
	2007	2008	2009
Never smoker	3,148 (55.6)	4,542 (54.1)	3,763 (54.1)
Current smoker	1,157 (20.4)	1,748 (20.8)	1,409 (20.3)
Former smoker	1,339 (23.6)	1,994 (23.8)	1,685 (24.2)
Total	**5,663 (43.7)**	**8,388 (59.5)**	**6,953 (57.4)**

Smoking status varied according to sex and age. Similar proportions of men and women were never smokers at 55.8% and 55.1%, respectively. Men had a higher percentage of former smokers (21.9 vs. 19.6%, p=0.001) and women had a higher percentage of current smokers (20.2 vs. 18.6%, p=0.015). Across the age spectrum, the percentage of patients who had never smoked dropped dramatically for men, from 99.6% of patients under 10 years old to 32.4% of patients aged at least 70 years old (Figure 4.5(a)). Women showed a more rapid drop-off in the 10 to 19 year old age range, but maintained a relatively stable rate of never smokers from age 20 onwards, ranging from 45.2 to 52.5%. Similar trends for men and women were noted for patients currently smoking (Figure 4.5(b)); however, among patients who had quit smoking, men had a higher rate than women for patients 60 years or older, at 55.3 vs. 38.9% (Figure 4.5(c)).



(a)



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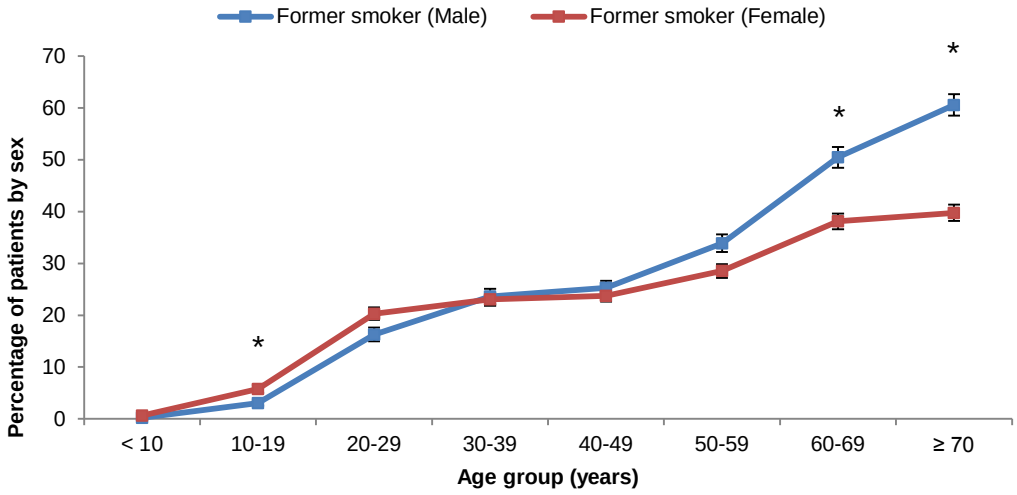


(c)

Figure 4.5: Age and sex distribution of patients with asthma in the FV database (2007 – 2009) for **(a)** never smokers, **(b)** current smokers and **(c)** former smokers

** p<0.05 for the difference between men and women*

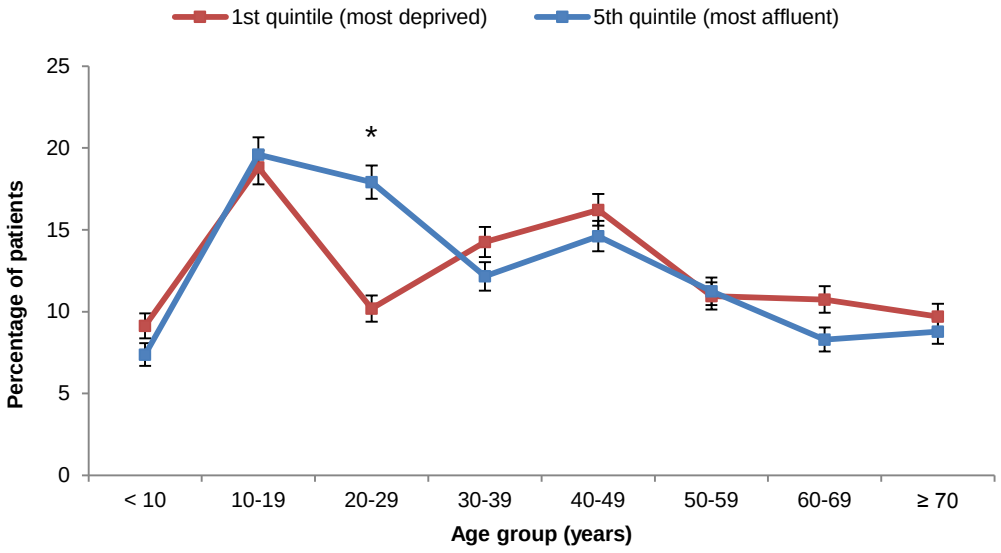
4.2.2.3 Deprivation

All 16,664 patients with asthma in the FV database had a SIMD score allocated based on their GP postcode. The patient population was relatively diverse with representation from both deprived and affluent areas, although there were slightly more than anticipated patients in more affluent quintiles, with imbalance primarily between 2nd and 3rd SIMD quintiles (Table 4.2). No differences between men and women were noted for deprivation classification.

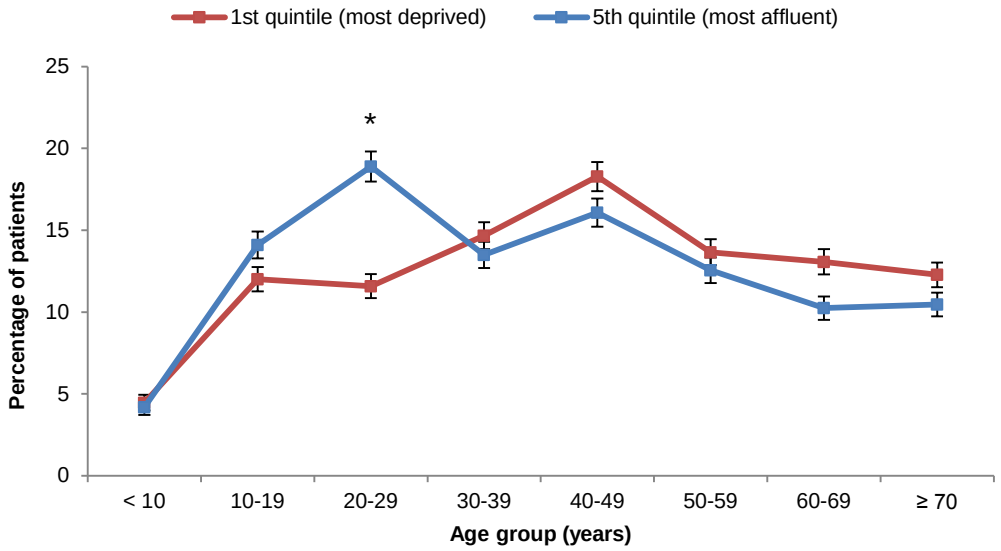
Table 4.2: SIMD quintile of patients with asthma in FV database by sex (2007 – 2009)

SIMD score	n (%)	
	Male	Female
1st quintile (most deprived)	1,424 (19.5)	1,882 (20.1)
2nd quintile	583 (8.0)	744 (7.9)
3rd quintile	2,293 (31.4)	2,948 (31.5)
4th quintile	1,575 (21.6)	1,976 (21.1)
5th quintile (most affluent)	1,423 (19.5)	1,816 (19.4)

The distribution of terminal SIMD categories according to age group was also relatively similar (Figure 4.6(a) and (b)), with an exception of both men and women aged 20 to 29 years old, where there were a higher proportion of affluent patients for both sexes.



(a)



(b)

Figure 4.6: Age and deprivation distribution of patients with asthma in the FV database (2007 – 2009) for **(a)** men and **(b)** women
** p<0.05 for the difference between men and women*

4.2.3 Discussion

In addition to the availability of data in both areas, it was thought that patient cohorts from NHS Forth Valley and Kentucky would provide for useful parallel analysis and comparison when applicable. Both areas are relatively rural, with a couple key but moderately-sized population areas. Additionally they are both rich in industrial occupational history, particularly with coal mining, which may be an important contributor to respiratory disease. Both Scotland and Kentucky are known to have

high rates of smokers compared to the UK and USA averages, respectively. Allergy burden is considered a significant contributor in Scotland compared to the rest of the UK (Anandan *et al.*, 2009), while several towns/cities in Kentucky have consistently featured in the most challenging areas of the USA to live with allergies (Asthma and Allergy Foundation of America, 2013). Overall health status is comparatively worse in these two areas compared to the country as a whole. Scotland has the highest mortality in Western Europe, thought to be associated with increased socioeconomic deprivation and other unknown issues; this disparity has been the subject of several publications and has been colloquially named the 'Scottish effect' or the 'Glasgow effect' (Scottish Public Health Observatory, 2013). Similarly, Kentucky is ranked 44th among states in the USA in regards to overall health, with smoking, preventable hospitalisation and premature death identified as significant area-specific challenges (United Health Foundation, 2013).

Despite similarities in their reference populations, the cohorts of patients with asthma from each area were different in terms of demographic distribution. Patients in the FV database were older than those in the KY database, although in both areas, the shape of the age distribution according to sex was similar with men peaking in prevalence earlier in life shifting to women peaking in later year. This distribution has been noted in several previous analyses (de Marco *et al.*, 2000; Nicolai *et al.*, 2003; Wirehn *et al.*, 2007). However, the median age difference between the FV and KY databases was particularly large and may suggest that asthma diagnoses are established earlier in the KY database, which identified 19.0% of patients under 10 years old, compared to 7.4% in the FV database. This may result from better recognition of the disease by clinicians or could suggest a greater burden of asthma in Kentucky as a result of the various causative factors associated with asthma including genetics, environment and allergen burden.

More likely, the demographic differences between the FV and KY databases are influenced by differences in the healthcare systems between countries. In the USA, when citizens reach 65 years of age and have worked and paid taxes, they are guaranteed access to medical insurance, albeit with varying levels of cost-share to the patient, administered by the USA government through Medicare; this includes prescription insurance through Medicare Part D. For these older patients, it is likely that they may only have insurance through Medicare and no other third-party carrier

or if they have third-party coverage, that they utilise Medicare as the primary biller. The first scenario could explain the lower proportions of older patients in the KY database and the second scenario could result in a lack of full capture of prescribed therapies for a particular patient depending on what coverage a particular service of prescription was processed. Unfortunately, the private administration of healthcare in the USA makes it difficult to form full population cohorts that are more readily accessible through the UK.

While other demographic information regarding the KY database was unavailable, the FV database was able to provide a more detailed profile regarding patients with asthma. Of particular note are the deprivation results, which demonstrate a relatively balanced socioeconomic background. The deprivation spread for practices in the FV database was similar to the health board as a whole and its three constituent local authorities (Figure 4.7). The Forth Valley area has a relatively balanced proportion of data zones in both deprived and affluent areas, compared to Glasgow and Edinburgh, which disproportionately reflect each end of the spectrum, respectively. This provides good evidence for the representativeness of the FV database patients compared to others across Scotland and the rest of the UK.

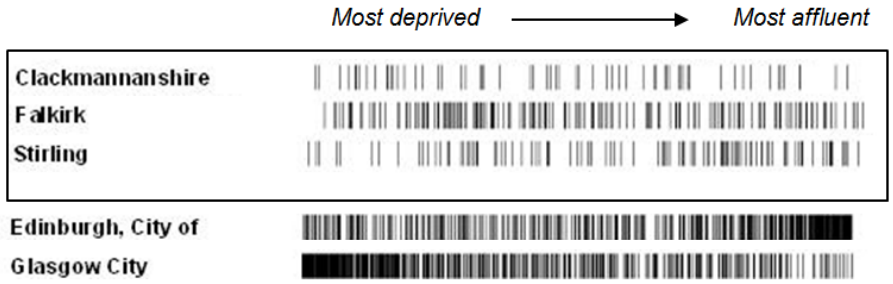


Figure 4.7: SIMD barcode profiles for data zones among local authorities in NHS Forth Valley with Glasgow and Edinburgh for comparison
Adapted from (The Scottish Government, 2009)

The SIMD score, however, is only valid for national comparison and provides no comparative basis with other countries. No similar comprehensive measure of socioeconomic deprivation is available in the USA but examination of various determinants may provide some insight. The American Community Survey (ACS) is a statistical survey conducted each year by the United States Census Bureau which collects a variety of demographic, social, economic and housing data (United States Census Bureau, 2014a). The most recent five-year survey estimates showed Kentucky to have lower educational attainment (85.7 vs. 82.4% achieving high

school graduation or higher), higher rates of disability (16.7 vs. 12.0%) and more families earning under the poverty level (14.2 vs. 10.9%) compared to national levels (United States Census Bureau, 2014b). How these figures relate to the population with asthma available in this database is unknown. This is particularly the case as the KY database was derived from a private insurance carrier and it would be reasonable to assume that the underlying population would be 'affluent' enough to be employed and able to afford such health care coverage.

A total of 19.5% of patients with asthma were identified as current smokers in the FV database which is lower than the average of the total NHS Forth Valley population at 26.9%, and Scotland as a whole at 26.5% (NHS Health Scotland, 2007). As asthma is not caused by smoking but can be significantly exacerbated if a patient continues to smoke, this reduced figure is expected. However, the nearly one-fifth of patients who continue to smoke despite having a diagnosis of asthma may be an area for development of patient education, as these patients are likely to experience the consequences of their smoking in a more direct manner with immediate breathlessness, rather than the long-term breathlessness induced by smoking in COPD. There may also be room for improvement with regards to clinician intervention with smoking behaviours, as only 40 to 60% of patients had a smoking status recorded within a given year. The QOF scheme aims for recording of a smoking status for both adolescents and adults every 15 months (Information Services Division Scotland, 2013b) which leaves room for some patients to remain un-captured with the yearly analysis performed on the FV database. However, clinician recording of smoking status and offering of cessation advice, if indicated, is an important aspect of clinical care for respiratory disease as well as general medical practice.

4.3 Medicine use trends

4.3.1 Methods

Prescription volume and defined daily dose

Each database was queried for respiratory medicines of interest. The raw number of prescriptions for each medicine in a given year was determined as well as the number of patients receiving prescriptions (queries 6 – 9); this was performed to better understand the inter- and intra-class preferences between databases. To compensate for differences in population size over time and between databases overall medicine utilisation was also calculated using DDDs. For each month during the three-year analysis, each distinct medicine, formulation and strength was queried and the number of doses prescribed/dispensed was determined (queries 10 – 11). The number of patients receiving treatment within the month of interest was also ascertained. The total amount (in mg) of medicine was calculated as a function of doses and strength and each corresponding medicine and formulation was matched with its DDD factor in the WHO database (World Health Organization, 2013a). The final overall metric for each medicine was calculated as previously described in Equation 3.2, with the number of patients with asthma substituted for the total population in the denominator.

The resulting estimates were plotted with trend lines for each graph to evaluate changes in utilisation over time. Beclometasone was split according to specific formulations to assess individual trends while other medicines (SABA, theophylline and OCS) were grouped according to class. Percentage change over the three-year period was estimated using the fitted trend equation. As DDDs are a metric for the assumed average dose in adults, this analysis was restricted to include patients greater than 12 years old as these patients are dosed as adults in asthma treatment guidelines (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2012). Additionally, the number of patients was utilised instead of the number of inhabitants as commonly employed for this metric in other analyses. This was due to both a lack of availability of full population data as well as an interest in measuring utilisation only by patients with asthma as opposed to the population at-large.

Prescribed daily dose

Prescribed daily dose (PDD), or the "*average dose prescribed according to a representative sample of prescriptions*", was also determined for ICS and combination therapy inhalers (World Health Organization, 2013b). For the FV database, the daily dose for each prescription was determined using a combination of inhaler strength and prescription instructions for dose and frequency (e.g. beclometasone 200 micrograms/puff inhaler at 2 puffs twice daily = 800 micrograms/day) (query 12). For the KY database no specific data on dose and frequency was available and therefore the daily dose was determined using the inhaler strength, doses per inhaler and day supply as a surrogate (e.g. fluticasone/salmeterol 250/50 microgram/puff inhaler with 60-dose inhaler and day supply of 30 days = 500 microgram/day) (query 13). In both databases there were a number of prescriptions where daily dose was unable to be determined either due to vague prescription instructions or a lack of prescription interval; these prescriptions were quantified and not included in the PDD calculation. Daily dose for each individual medicine was calculated and averaged with some medicines split by formulation as in the DDD calculation. Results were reported as both an overall three-year average although yearly averages were calculated to assess any temporal change. Separate analyses were conducted for adults/adolescents (greater than 12 years old) and children (5 to 12 years old) to align with dose cut-off recommendations in the BTS/SIGN guideline (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2012). For comparison of mean doses across databases a two-sample t-test was used, and differences between groups within each database were assessed with a one-way analysis of variance (ANOVA) and Tukey's test as a multiple comparison procedure. The grouping of statistical differences resulting from Tukey's test were marked with letters (A, B, C…), with groups sharing a common letter being statistically similar, and groups with different letters statistically different.

Adherence and persistence

Adherence for maintenance medicines was assessed using the medication possession ratio (MPR) which is a measure of the number of days that a medicine is available to a patient for treatment, and was calculated using Equation 4.1:

Equation 4.1:

$$\text{MPR} = \frac{\text{number of days of available medicine}}{\text{time between first/last prescription}} * 100\%$$

Prescriptions for maintenance medications issued between January 2007 and December 2009 were assessed including ICS, combination therapy inhalers, LABA and theophylline for the FV database and ICS, combination therapy inhalers, LABA, theophylline and LTRA for the KY database (queries 14 – 15). The number of days of available medicine was calculated according to the prescription posology and inhaler size (e.g. 60-dose inhaler with prescription instructions of 1 puff twice daily = 30 day supply) for the FV database and using the days' supply column submitted for the prescription claim in the KY database. A sequence of at least two prescriptions for each patient was required to calculate the MPR. The calculation was specific to therapeutic class, but not to dose or individual pharmacological agent. Thus, a patient receiving sequential treatment with two different ICS inhalers (e.g. fluticasone switched to beclometasone) or having a change in the fluticasone dose mid-therapy would have a single MPR calculation. However, a patient may have multiple MPRs if they received medications from more than one therapeutic class, such as treatment with an ICS changed to treatment with a combination therapy inhaler or simultaneous treatment with both an ICS and a LABA; the analysis was conducted this way to capture different medicine use behaviours that may occur within a single patient depending on the medication such as regular receipt of an ICS but simultaneous intermittent use of the LABA. The amount of SABA (in doses/day) prescribed during each MPR was also quantified. This was achieved by summing the number and size of SABA inhalers to determine the total number of SABA doses prescribed and then dividing by the number of days over which the controller inhaler was prescribed – the denominator of the MPR calculation (query 16).

MPRs were reported with median and interquartile ranges and compared using a Kruskal-Wallis test. As a patient may receive more medication supply than technically needed to cover their treatment (due to overlapping prescriptions or extra inhalers) the MPR has no upper limit and may overestimate adherence as a continuous measure. The MPR was further classified into three standard categories including undersupply (less than 80%), adequate supply (80 to 120%) and oversupply (greater than 120%) (Karve *et al.*, 2009; Krigsman, Nilsson*, et al.*, 2007). Results were also stratified by patient age, sex and therapeutic class of medicine prescribed.

Persistence for chronic medicines was evaluated using a refill sequence model (Caetano *et al.*, 2006) which was calculated as the difference in time between the first prescription for a medicine and either the last prescription for that medicine or a gap in therapy (whichever occurred first). An acceptable gap was set at less than 30 days after the previous supply of medication was due to run out although a sensitivity analysis assessed increasing this threshold to 60 and 90 days. As the FV database collected patient data on a rolling basis, patients may have had a therapy gap in the database either due to cessation of treatment or simply because their practice stopped recording data. As such, persistence was assessed for therapies started in 2008 and patients must have had prescription data present in the database after what was considered their terminal date (the last prescription or the first gap in therapy) thus proving their continued presence and confirmed cessation of treatment (queries 17 – 18). Included patients were a mix of those on both new and prevalent therapy, meaning they may have received therapy prior to the start window of analysis in 2008.

Persistence was reported as both mean and median time to discontinuation (TTD), and results were displayed using a Kaplan-Meier survival plot with a time sensor utilised at 365 days to determine one-year persistence rates. As with adherence, persistence was stratified by therapeutic class and patient age and sex.

4.3.2 Results

4.3.2.1 Prescription volume

A total of 342,047 prescriptions were issued to 16,645 patients with asthma in the FV database during 2007 – 2009 (Table 4.3(a)). Overall volume was highest in 2007 and 2008, dropping off in 2009 due to phasing-out of the database tool in GP practices for data collection. Salbutamol was overwhelmingly the preferred choice for SABA therapy with terbutaline volume at approximately one-tenth of salbutamol. Among ICS inhalers, generic/CFC-containing/DPI BDP (labelled as plain 'beclometasone' hereafter) and Clenil Modulite® (HFA-BDP) were most common, followed by fluticasone: a third formulation of beclometasone, Qvar® (extra fine HFA-BDP), was utilised infrequently. Seretide® (fluticasone/salmeterol) constituted the majority of combination therapy inhalers with approximately three times the volume of Symbicort® (budesonide/formoterol). ICS (cumulatively) constituted the largest number of prescriptions for maintenance therapy of therapies assessed.

Table 4.3a: Prescription volume of selected medicines for patients with asthma (2007 – 2009) in the FV database
† *including generic, CFC-containing, and DPI formulations of BDP*

Medicine	Prescriptions (patients), n		
	2007	2008	2009
Salbutamol	56,361 (10,378)	52,906 (11,487)	36,216 (9,531)
Terbutaline	5,725 (1,451)	5,352 (1,529)	3,760 (1,239)
Beclometasone †	14,135 (3,486)	7,636 (2,701)	2,973 (1,194)
Clenil Modulite® (HFA-BDP)	3,238 (1,293)	8,475 (2,734)	6,969 (2,532)
Qvar® (extra fine HFA-BDP)	1,446 (389)	2,041 (557)	1,458 (529)
Budesonide	4,308 (1,059)	4,125 (1,152)	2,616 (897)
Fluticasone	6,349 (1,181)	5,469 (1,244)	3,235 (938)
Ciclesonide	204 (46)	162 (47)	84 (36)
Mometasone	74 (17)	83 (20)	34 (15)
Seretide® (fluticasone/salmeterol)	21,856 (3,319)	21,029 (3,867)	15,737 (3,594)
Symbicort® (budesonide/formoterol)	4,879 (908)	5,601 (1,159)	4,589 (1,148)
Salmeterol	5,445 (903)	4,429 (934)	2,724 (710)
Formoterol	409 (63)	406 (68)	199 (52)
Theophylline	2,246 (278)	1,965 (296)	1,357 (270)
Prednisolone	3,669 (1,634)	5,713 (2,478)	4,360 (1,957)
Total	**130,344 (12,912)**	**125,392 (14,059)**	**86,311 (12,090)**

A total of 50,090 prescriptions were issued to 6,420 patients in the KY database from 2007 – 2009 (Table 4.3(b)). Prescription volume was relatively stable across all three years. Albuterol (known as salbutamol in the UK) was the most frequently utilised SABA inhaler, although levalbuterol was also commonly used. Budesonide was the preferred choice of ICS inhaler although there was a widespread of use of other ICS inhalers, particularly fluticasone. Advair® (fluticasone/salmeterol) constituted the majority of combination therapy inhalers and formoterol was the most commonly used LABA inhaler. Combination therapy inhalers represented the largest utilised inhaled therapeutic class of medication.

Table 4.3b: Prescription volume of selected medicines for patients with asthma (2007 – 2009) in the KY database

Medicine	Prescriptions (patients), n		
	2007	2008	2009
Albuterol	4,063 (1,933)	3,796 (1,881)	3,928 (1,965)
Pirbuterol	92 (61)	88 (58)	70 (51)
Levalbuterol	748 (361)	892 (403)	939 (399)
Mometasone	377 (136)	496 (159)	565 (176)
Triamcinolone	44 (28)	54 (34)	49 (25)
Budesonide	583 (310)	605 (282)	648 (273)
Fluticasone	597 (220)	483 (196)	449 (203)
Qvar® (extra fine HFA-BDP)	172 (63)	206 (79)	181 (78)
Advair® (fluticasone/salmeterol)	3,098 (975)	2,745 (867)	2,664 (793)
Symbicort® (budesonide/formoterol)	61 (34)	400 (155)	644 (252)
Salmeterol	91 (20)	69 (21)	25 (10)
Formoterol	223 (67)	204 (52)	105 (33)
Theophylline	267 (50)	279 (54)	239 (44)
Montelukast	6,113 (1,411)	5,682 (1,378)	5,158 (1,224)
Prednisone	1,455 (922)	1,645 (1,000)	1,750 (1,064)
Total	**18,221 (3,365)**	**16,106 (3,448)**	**15,763 (3,371)**

4.3.2.2 Defined daily dose

SABA utilisation (both salbutamol and terbutaline) in the FV database decreased 30.1% during the observation period, having a high of 1,111 DDDs in February 2007 and a low of 739 DDDs in October 2009 (Figure 4.8). Overall SABA utilisation (albuterol, pirbuterol and levalbuterol) in the KY database was approximately one-fifth that in the FV database but with a smaller decrease of 17.1% ranging from a high of 213 in January 2007 to a low of 126 DDDs in January 2009; an outlier was noted at 263 DDDs in December 2009.

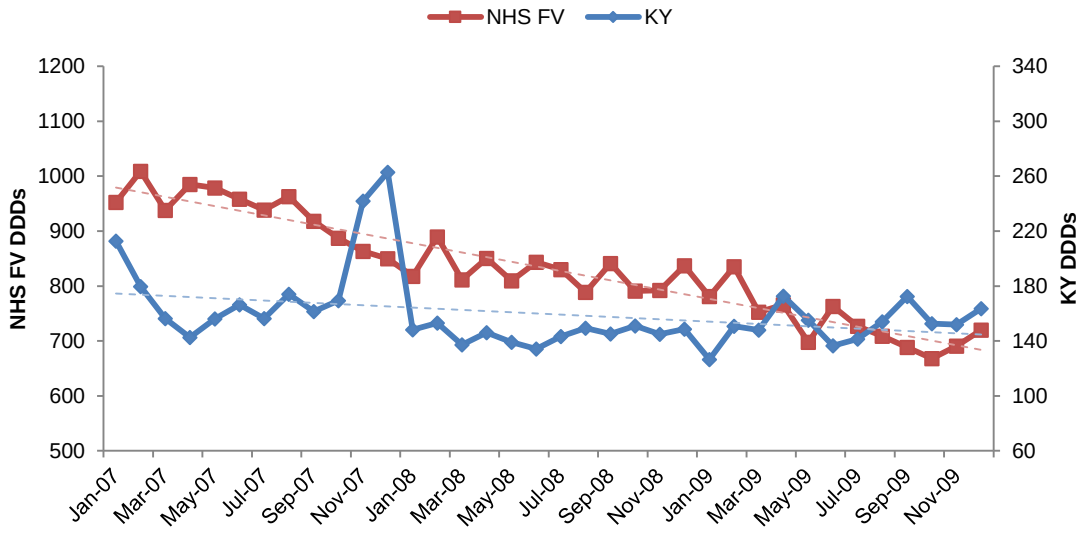


Figure 4.8: DDDs per 1,000 patients with asthma per day for SABAs in the FV and KY databases (2007 – 2009)

In the FV database, beclometasone was the most commonly prescribed ICS although the three different formulations were subject to different longitudinal trends. The use of beclometasone decreased by 94.3% during 2007 – 2009, from a high of 331 DDDs in February 2007 to a low of 57 DDDs by December 2009 (Figure 4.9). Clenil Modulite® was licensed during the same time frame. Prescribing started at 17 DDDs in January 2007 and increased to 206 DDDs by December 2009. Increases were apparent in 2007 and 2008, which levelled off during 2009. Qvar® utilisation increased by 25.1% during the observation period, ranging from 16 DDDs in September 2007 to 30 DDDs in December 2008 (Figure 4.10). Increased utilisation predominately occurred in 2007 and 2008 with a drop-off noted throughout 2009. In the KY database, only Qvar® was utilised although to a very low degree and increased by 9.4% ranging from 0.7 DDDs in February 2007 to 3 DDDs in September 2007 (as well as an outlier at 5 DDDs in December 2007).

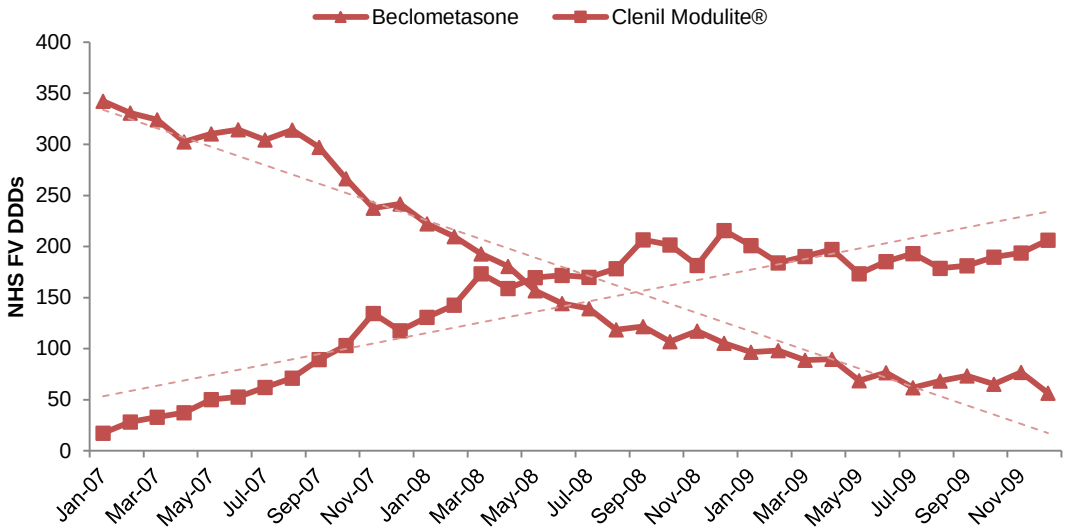


Figure 4.9: DDDs per 1,000 patients with asthma per day for generic/CFC-containing formulations (beclometasone) and Clenil Modulite® in the FV database (2007 – 2009)

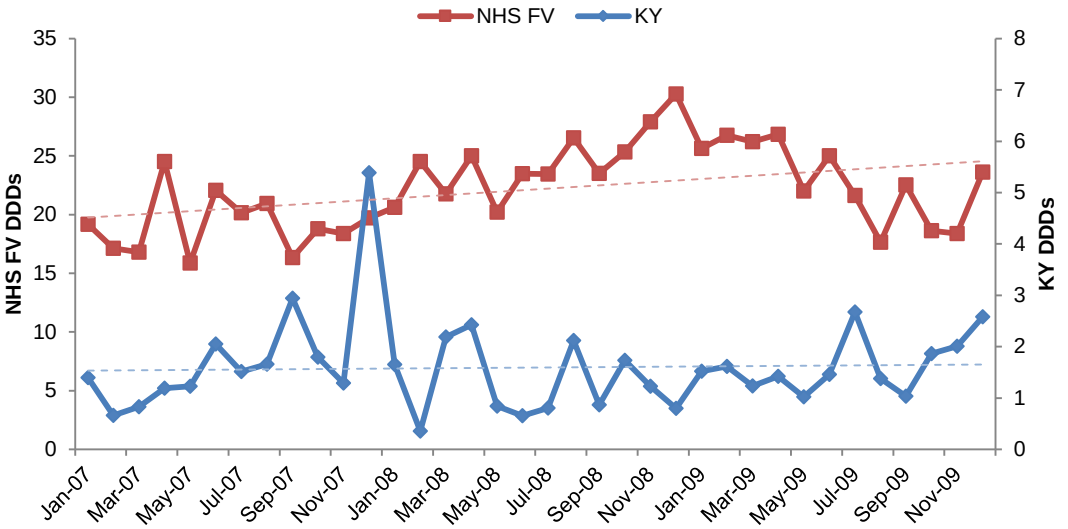


Figure 4.10: DDDs per 1,000 patients with asthma per day for Qvar® in the FV and KY databases (2007 – 2009)

Use of budesonide in the FV database decreased by 26.6% from a high of 96 DDDs in March 2007 to a low of 58 DDDs in August 2009 (Figure 4.11). Despite being the most utilised individual ICS, use of budesonide also decreased in the KY database by a margin of 29.9%. Overall usage was approximately one-fifth that of the FV database and ranged from a high of 16 DDDs in February 2007 (with an outlier of 23 DDDs in January 2007) to a low of 10 DDDs in July 2007.

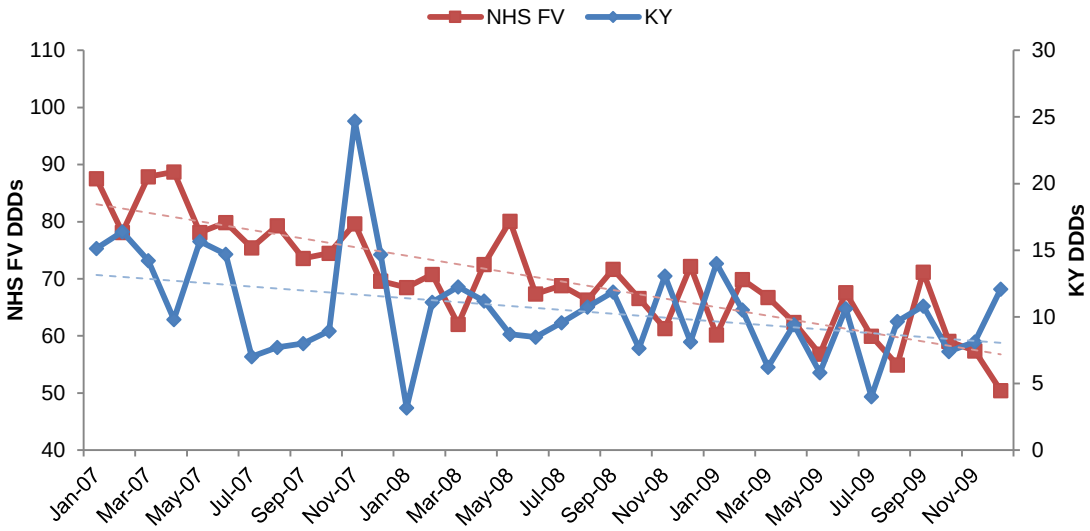


Figure 4.11: DDDs per 1,000 patients with asthma per day for budesonide in the FV and KY databases (2007 – 2009)

Fluticasone in the FV database was subject to a steady decrease in utilisation of 50.3%, with a high of 144 DDDs in March 2007 and a low of 65 DDDs in July 2009 (Figure 4.12). In the KY database, fluticasone utilisation was a fraction of that of the FV database and was also subject to a 51.2% decrease in use over the observation period with a high of 20 DDDs in October 2007 (with outlying 35 DDDs in December 2007) and a low of 11 DDDs in October 2009.

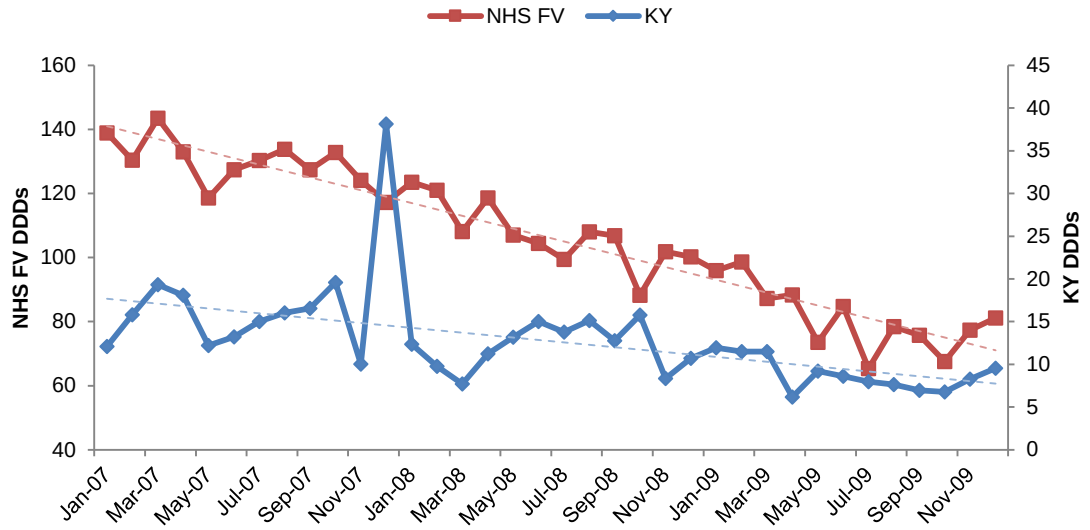


Figure 4.12: DDDs per 1,000 patients with asthma per day for fluticasone in the FV and KY databases (2007 – 2009)

Overall utilisation of ICS decreased in both databases although the decrease was more pronounced in the FV database (35.8%) compared to the KY database (18.1%) (Figure 4.13). For the FV database, utilisation ranged from 619 DDDs in August 2007 to 395 DDDs in May 2009: in the KY database, it ranged from 58 DDDs in June 2008 (with outlying 86 DDDs in December 2009) to 35 DDDs in October 2009.

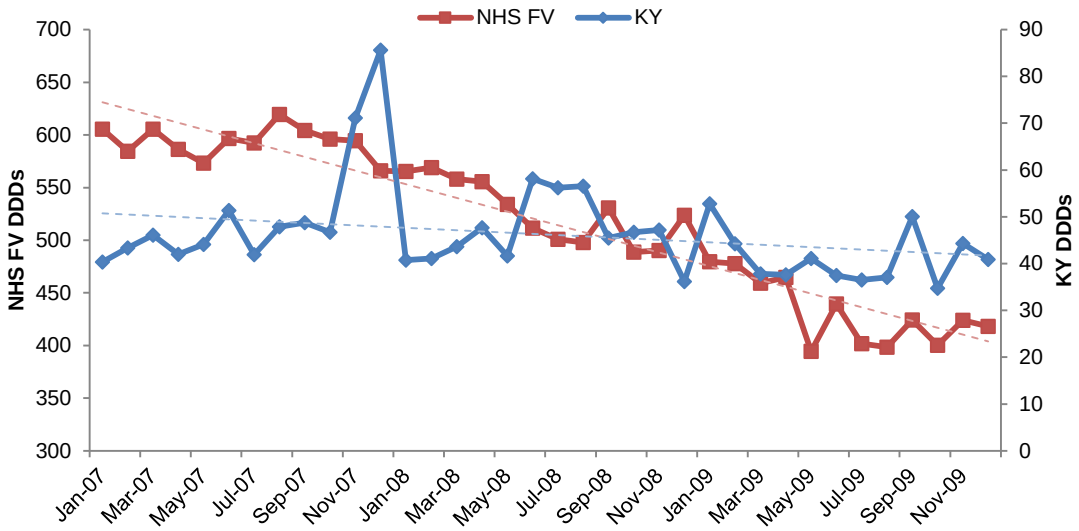


Figure 4.13: DDDs per 1,000 patients with asthma per day for total ICS in the FV and KY databases (2007 – 2009)

For LABA inhalers, utilisation also decreased in both databases (Figure 4.14). In the FV database, total LABA utilisation decreased by 50.3% from a peak of 120 DDDs in February 2007 to a low of 57 DDDs in December 2009. In the KY database, LABA utilisation was approximately one-tenth that of the FV database, and decreased by 41.1% from a high of 22 DDDs in November and December 2007 to a low of 4 DDDs in April 2009.

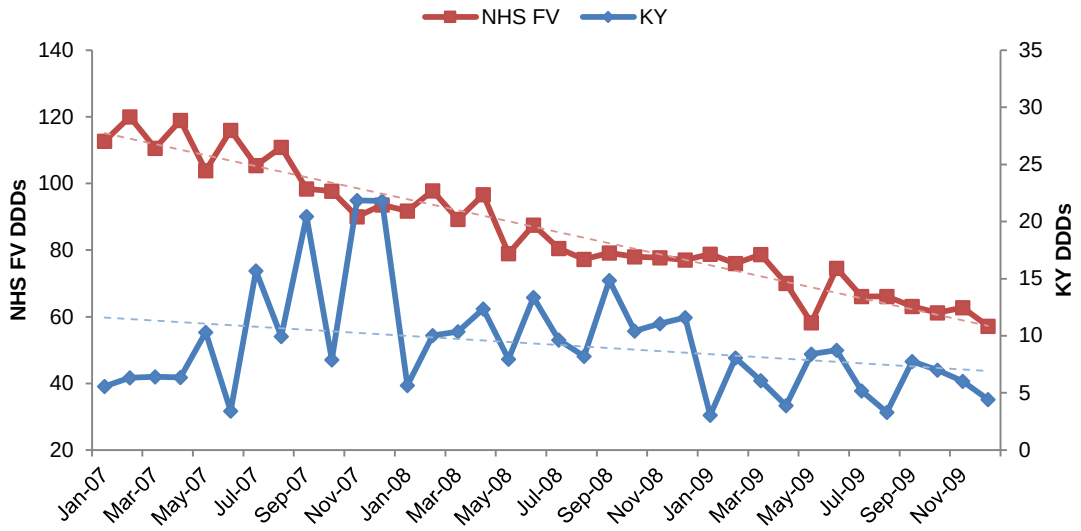


Figure 4.14: DDDs per 1,000 patients with asthma per day for total LABA in the FV and KY databases (2007 – 2009)

Fluticasone/salmeterol (Seretide®) utilisation in the FV database showed a steady downward trend of 17.5%; use fluctuated from a high of 460 DDDs in February 2007 to a low of 337 DDDs in October 2009 (Figure 4.15). Fluticasone/salmeterol (Advair®) utilisation in the KY database similarly decreased (by 26.4%) although with a relatively stable downward trend across the three years, having a high of 191 DDDs in April 2007 (with an outlier of 207 DDDs in December 2007) and a low of 117 DDDs in November 2009.

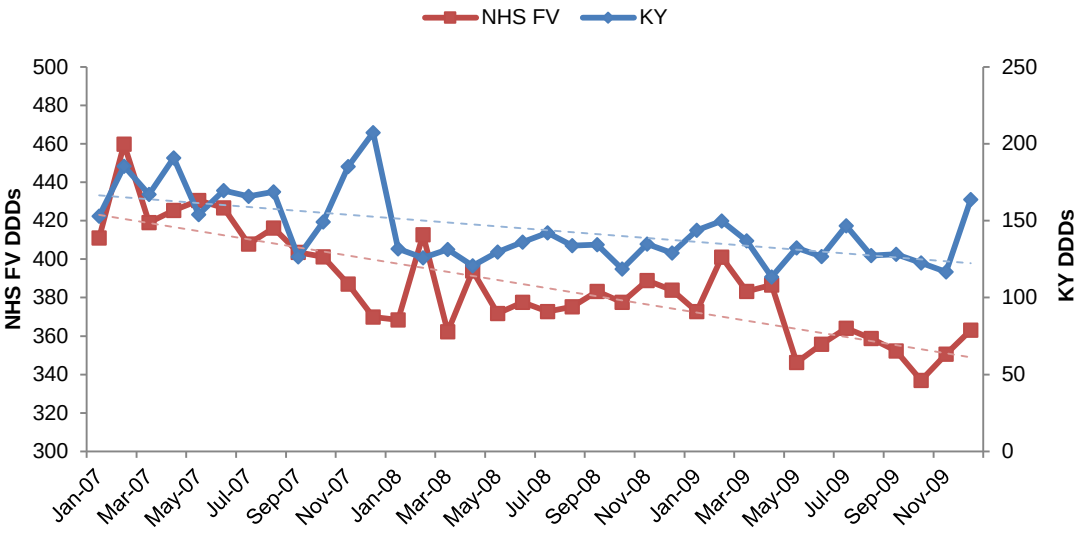


Figure 4.15: DDDs per 1,000 asthma patients per day for fluticasone/salmeterol in the FV and KY databases (2007 – 2009)

Overall use of budesonide/formoterol in the FV database increased 26.7% with a low of 88 DDDs in July 2007 and a high of 130 DDDs in June 2009 (Figure 4.16). The use of budesonide/formoterol started during the observation period in the KY database, beginning in July 2007 and steadily increased to a high of 40 DDDs in September 2009.

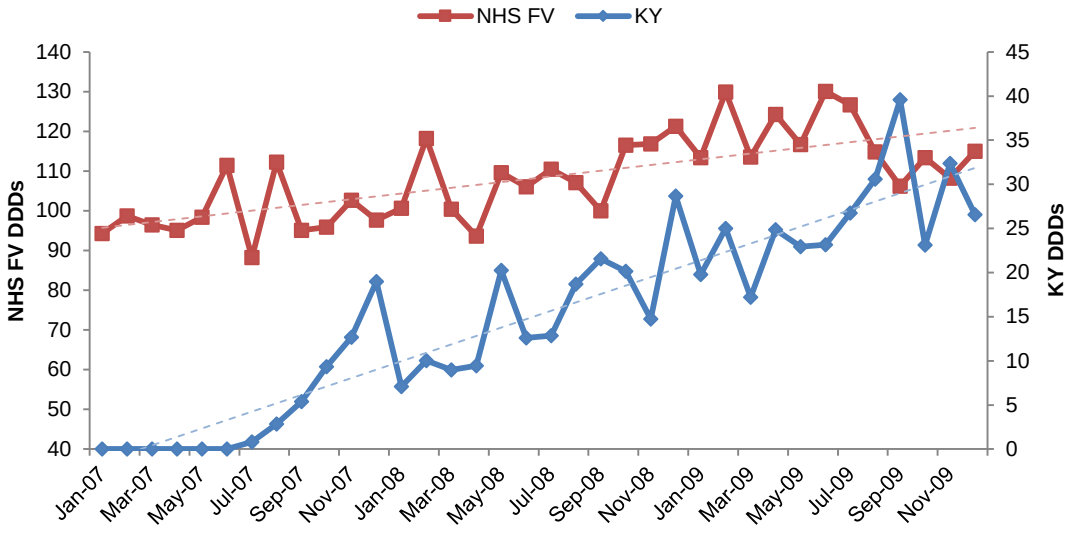


Figure 4.16: DDDs per 1,000 patients with asthma per day for budesonide/formoterol in the FV and KY databases (2007 – 2009)

Theophylline use decreased by 52.6% in the FV database from a high of 74 DDDs in February 2007 and a low of 24 DDDs in October 2009 (Figure 4.17). The use of theophyllines in the KY database was lower but more stable with a slight increase over time at 10.5%, and a high of 23 DDDs in July 2009 and low of 7 DDDs in September 2007.

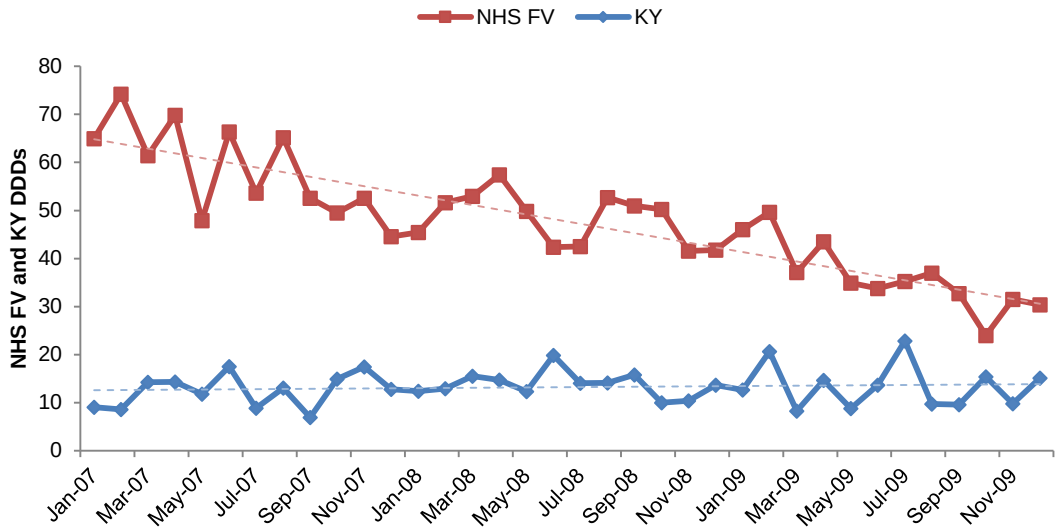


Figure 4.17: DDDs per 1,000 patients with asthma per day for theophylline in the FV and KY databases (2007 – 2009)

LTRAs in the KY database decreased by 24.8%, with a high of 287 DDDs in April 2009 and a low of 192 DDDs in November 2009; a distinct outlier was noted at 407 DDDs in November 2007 (Figure 4.18). The use of LTRAs in the FV database was unable to be determined, as these data were not collected.

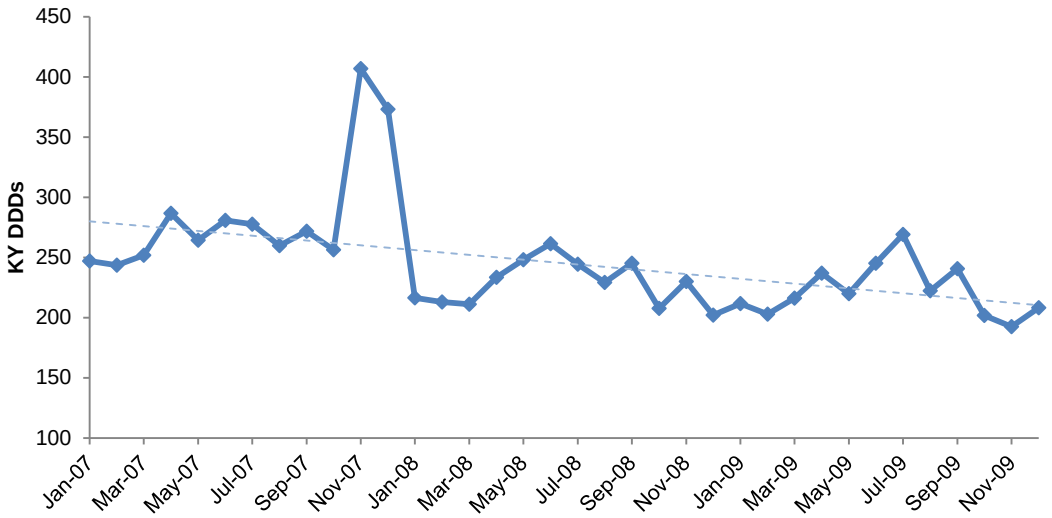


Figure 4.18: DDDs per 1,000 asthma patients per day for LTRAs in the KY database (2007 – 2009)

The use of prednisolone in the FV database increased by 57.6% from a low of 23 DDDs in May 2007 to a high of 76 DDDs in December 2008, although stabilisation was apparent in 2009 onward (Figure 4.19). The use of prednisone in the KY database was higher and more variable overall although increased more slowly by 21.1% during the observation period, having a low of 33 DDDs in April 2007 and a high of 129 DDDs in December 2008. Spikes in utilisation were seen in winter months in both 2007 and 2008.

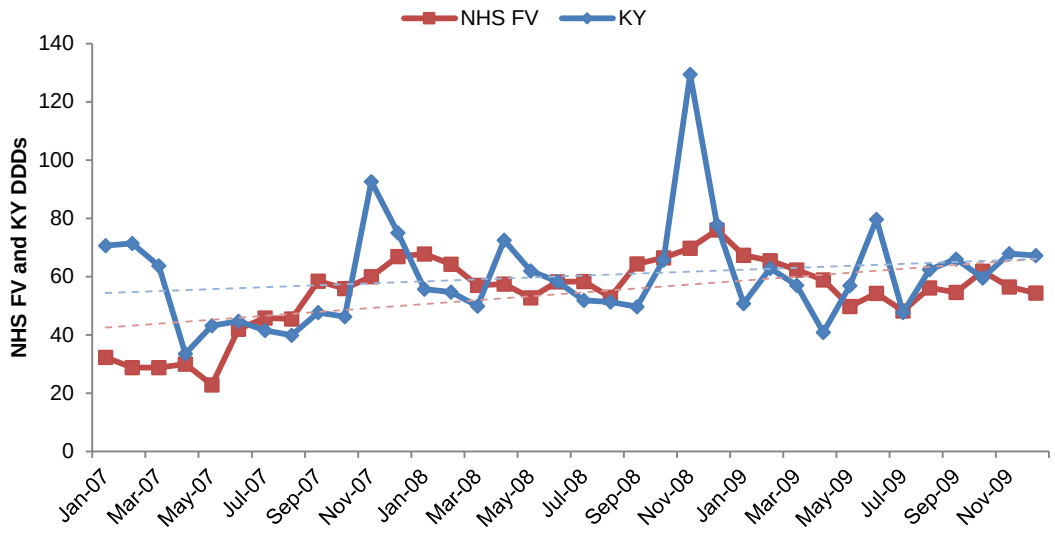


Figure 4.19: DDDs per 1,000 asthma patients per day for OCS in the FV and KY databases (2007 – 2009)

4.3.2.3 Prescribed daily dose

The three-year mean daily dose for ICS-containing inhalers varied according to medicine/formulation. For adults and adolescents in the FV database, budesonide/formoterol had the highest overall dose and Qvar® had the lowest dose at 736.9 micrograms/day and 266.1 micrograms/day, respectively (Table 4.4(a)). Despite having twice the dose potency, both fluticasone and fluticasone/salmeterol were utilised at similar or higher doses than beclometasone, budesonide and Clenil Modulite®. When adjusted for potency differences and classified according to dose categories within the BTS/SIGN asthma guideline, the mean doses of all assessed medicines were classified as medium-dose, with the exception of fluticasone and fluticasone/salmeterol which were considered high-dose. For children, budesonide/formoterol similarly had the highest dose and Qvar® the lowest dose at 406.8 micrograms/day and 157.0 micrograms/day respectively. The dose of fluticasone relative to its comparators was reduced and less than that of

beclometasone, budesonide and Clenil Modulite® but still higher than that of similar potency Qvar®. All mean medicine doses were classified as medium-dose, except fluticasone/salmeterol which was high-dose. A total of 7,716 (5.2%) prescriptions in the FV database were unable to have a daily dose calculated.

Table 4.4a: PDD of ICS and combination therapy inhalers for patients with asthma in the FV database
Letters indicate statistical grouping based on Tukey's method (A = highest dose and E = lowest dose), analysed separately for adults/adolescents and children

Medicine (n=number of prescriptions for each group)	Adult/adolescents, dose (SEM) in mcg	Children, dose (SEM) in mcg
Beclometasone (n=21,076/3,027)	568.1 (3.2)[D]	268.8 (3.4)[C]
Clenil Modulite® (n=14,698/3,065)	559.5 (3.1)[D]	269.4 (4.7)[C]
Qvar® (n=4,619/279)	266.1 (2.4)[E]	157.0 (5.8)[E]
Budesonide (n=9,817/1,060)	625.7 (6.2)[C]	311.2 (6.7)[B]
Fluticasone (n=13,775/1,138)	628.3 (4.4)[C]	180.3 (3.2)[D]
Fluticasone/salmeterol (n=56,425/2,143)	686.6 (2.8)[B]	267.0 (3.4)[C]
Budesonide/formoterol (n=14,679/387)	736.9 (2.5)[A]	406.8 (9.2)[A]

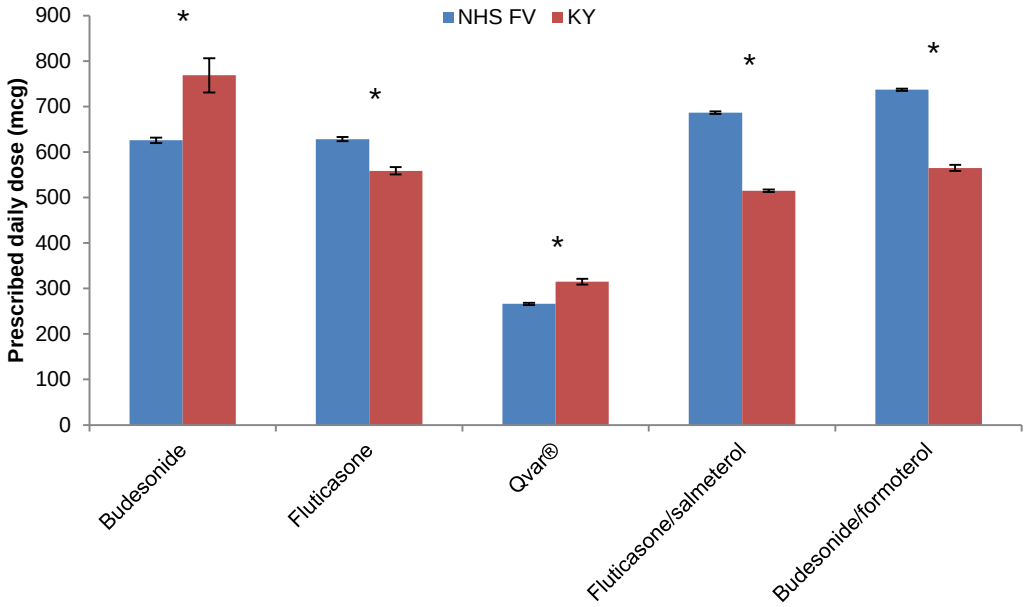
In adults/adolescents in the KY database, budesonide had the highest three-year mean dose at 768.5 micrograms/day, and Qvar® had the lowest dose at 315.0 micrograms/day (Table 4.4(b)). Fluticasone, mometasone and fluticasone/salmeterol, despite having a higher potency, had a similar or higher mean daily dose compared to budesonide/formoterol. While the mean doses for Qvar®, budesonide and budesonide/formoterol were classified as medium-dose, doses for fluticasone, mometasone and fluticasone/salmeterol were classified as high-dose. For children, doses were not reduced compared to adults with budesonide remaining the highest with 683.6 micrograms/day and Qvar® the lowest with 200.9 micrograms/day. A similar dose relationship among ICS inhalers was noted for children compared to adults/adolescents, with the exception of budesonide/formoterol which was not used in the KY database for children and therefore was unable to be assessed. All mean doses for medicines for children in

the KY database were high-dose, although the estimates were more variable as seen by increased standard error of the mean (SEM). A total of 24 (0.2%) prescriptions were unable to have a daily dose calculated in the KY database.

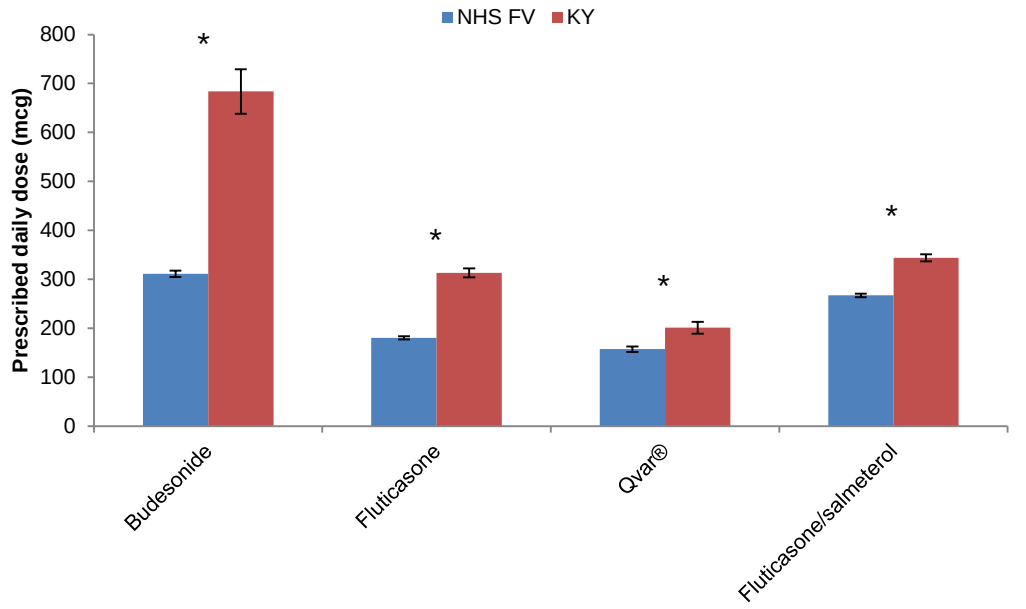
Table 4.4b: PDD of ICS and combination therapy inhalers for patients with asthma in the KY database
Letters indicate statistical grouping based on Tukey's method (A = highest dose and D = lowest dose), analysed separately for adult/adolescents and children

Medicine (n=number of prescriptions for each group)	Adult and adolescents, dose (SEM) in mcg	Children, dose (SEM) in mcg
Qvar® (n=328/174)	315.0 (6.3)[D]	200.9 (12.1)[D]
Budesonide (n=516/158)	768.5 (37.6)[A]	683.6 (45.5)[A]
Fluticasone (n=869/483)	558.6 (8.1)[C]	313.0 (8.9)[C]
Mometasone (n=1,208/247)	659.6 (9.7)[B]	505.8 (37.1)[B]
Fluticasone/salmeterol (n=7,980/523)	514.8 (2.9)[C]	343.6 (7.2)[C]
Budesonide/formoterol (n=1,056/0)	565.0 (6.5)[C]	N/A

PDD estimates were also compared between the FV and KY databases (Figure 4.20(a) and (b)). For adults/adolescents, higher doses of fluticasone, fluticasone/salmeterol and budesonide/formoterol were utilised in the FV database compared to the KY database. For children, doses for all ICS and combination therapy inhalers were higher in the KY database – some with a significant difference such as budesonide with margin of 372.4 micrograms.



(a)



(b)

Figure 4.20: Comparison of PDD of ICS and combination therapy inhalers in the FV and KY databases for **(a)** adults and **(b)** children with asthma (2007 – 2009)
** p<0.01 for the difference between databases*

4.3.2.4 Adherence

A total of 13,730 and 3,463 episodes of chronic medicine use were assessed for adherence for 11,589 and 2,577 patients in the FV and KY databases respectively. The overall median medication possession ratio (MPR) in the FV database was 75.1% (IQR: 44.6 to 114.4%), with men having a higher median MPR than women (78.1 vs. 73.4%, $p<0.001$). Overall 53.3% of MPRs were classified as undersupply with the remainder broadly split between adequate supply (24.1%) and oversupply (22.6%). Among these patients, 9,693 (83.6%) were treated with a single therapeutic class during the period assessed. The overall median MPR in the KY database was 55.6% (IQR: 32.1 to 82.4%) and no difference was seen between men and women (56.8 vs. 54.5%, $p=0.161$). Nearly three-quarters (72.8%) of MPRs were classified as undersupply, with nearly all remaining MPRs (25.9%) as adequate supply; only 1.3% of MPRs were classified as oversupply. A total of 1,769 (68.6%) patients were treated with a single therapeutic class.

The median MPR in the FV database increased with age, from a low of 61.3% (IQR: 34.2 to 101.5%) for patients 10 to 19 years old to 87.6% (56.8 to 118.0%) for patients 70 years and older; the median MPR for children less than 10 years old was distinct from this trend at 78.7%, approximating that of patients aged 50 to 59 years old. Children less than 10 years old had the highest proportion of oversupply (MPR greater than 120%) among all age groups, while patients 10 to 19 years old had the lowest proportion (Table 4.5(a)). An increasing proportion of adequate medication supply (MPR 80 to 120%) and a decreasing proportion of undersupply (MPR less than 80%) were otherwise maintained with increasing age.

Table 4.5a: Medication supply by MPR classification for patients with asthma by age group (2007 – 2009) in the FV database

Age (years)	Undersupply n (%)	Adequate supply n (%)	Oversupply n (%)
< 10	667 (50.7)	290 (22.0)	359 (27.3)
10-19	1,095 (63.2)	323 (18.7)	314 (18.1)
20-29	860 (58.9)	294 (20.1)	306 (21.0)
30-39	1,112 (55.2)	434 (21.6)	467 (23.2)
40-49	1,300 (54.6)	529 (22.2)	551 (23.2)
50-59	1,033 (51.2)	520 (25.8)	463 (23.0)
60-69	716 (45.6)	511 (32.6)	343 (21.8)
≥ 70	539 (43.4)	410 (33.0)	293 (23.6)

For the KY database, the median MPR also increased with age, from a low of 45.3% (IQR: 26.3 to 69.3%) for patients aged 10 to 20 years old to a higher of 70.5% (IQR: 38.3 to 94.4%) for patients aged 60 to 69 years old. Patients younger than 10 years of age were again distinct from this trend with a median MPR of 29.1%, as were patients aged 70 years and older at 55.7%. Trends in median MPR were closely mirrored by the classification of medicine supply as the influence of oversupply was insignificant (Table 4.5(b)).

Table 4.5b: Medication supply by MPR classification for patients with asthma by age group (2007 – 2009) in the KY database

Age (years)	Undersupply n (%)	Adequate supply n (%)	Oversupply n (%)
< 10	756 (76.8)	211 (21.4)	17 (1.7)
10-19	439 (81.9)	93 (17.4)	4 (0.8)
20-29	185 (71.4)	71 (27.4)	3 (1.2)
30-39	339 (76.7)	99 (22.4)	4 (0.9)
40-49	381 (69.2)	164 (29.8)	6 (1.1)
50-59	287 (62.7)	163 (35.6)	8 (1.8)
60-69	112 (56.6)	82 (41.9)	3 (1.5)
≥ 70	22 (62.9)	12 (34.3)	1 (2.9)

According to therapeutic class in the FV database, theophylline had the highest median MPR at 99.3% (IQR: 80.9 to 127.0%) distinct and separate from the other therapies assessed, which ranged from 68.0% (IQR: 42.1 to 101.1%) for LABAs to

77.4% (IQR: 48.7 to 111.1%) for combination therapy inhalers (p<0.001). There was an indication that this was partially influenced by a larger proportion of medication oversupply for theophylline compared to other therapies; however, theophylline also had approximately half the degree of undersupply seen within ICS, LABA and combination therapy inhalers (Table 4.6(a)).

Table 4.6a: Medication supply by MPR classification for patients with asthma by therapeutic class (2007 – 2009) in the FV database

Therapeutic class	Undersupply n (%)	Adequate supply n (%)	Oversupply n (%)
ICS	4,124 (54.1)	1,627 (21.4)	1,871 (24.6)
LABA	602 (59.5)	251 (24.8)	159 (15.7)
CMB	2,540 (52.2)	1,333 (27.4)	993 (20.4)
TP	57 (24.8)	100 (43.5)	73 (31.7)

Among therapeutic classes in the KY database, theophylline and LTRA had similarly high median MPRs at 79.9% (IQR: 51.3 to 93.6%) and 70.3% (IQR: 44.9 to 90.4%), respectively compared to other therapies assessed (p<0.001); median MPR for the remaining inhaled therapies ranged from 37.6% (IQR: 20.0 to 63.5%) for ICS to 46.9% (IQR: 29.7 to 75.2%) for LABA. Again, the classification of medicine supply reflected the median MPRs well due to a low degree of oversupply (Table 4.6(b)).

Table 4.6b: Medication supply by MPR classification for patients with asthma by therapeutic class (2007 – 2009) in the KY database

Therapeutic class	Undersupply n (%)	Adequate supply n (%)	Oversupply n (%)
ICS	631 (86.1)	84 (11.5)	18 (2.5)
LABA	41 (78.9)	11 (21.1)	0 (0.0)
CMB	825 (82.2)	169 (16.8)	10 (1.0)
TP	18 (50.0)	18 (50.0)	0 (0.0)
LTRA	1,006 (61.4)	614 (37.5)	18 (1.1)

Overall, 91.2% of episodes for chronic medication in the FV database were accompanied by treatment with a SABA, with a median of 2.6 doses/day (IQR: 1.2 to 5.0 doses/day). The number of doses/day increased with MPR category, with the median prescribing of SABA for patients with undersupply at 1.8 doses/day (IQR: 1.0 to 3.6 doses/day), with adequate supply at 3.1 doses/day (IQR: 1.4 to 5.7

doses/day) and with oversupply at 5.3 doses/day (IQR: 2.6 to 9.6 doses/day) ($p<0.001$ for comparison). Only 46.5% of episodes in the KY database recorded concurrent treatment with a SABA, with a lower median use of 1.2 doses/day (IQR: 0.6 to 2.7 doses/day). Doses/day again correlated with MPR, increasing from a median of 1.1 doses/day (IQR: 0.6 to 2.6 doses/day) for undersupply, 1.4 doses/day (IQR: 0.7 to 6.8 doses/day) for adequate supply and 8.3 doses/day (IQR: 3.3 to 6.8 doses/day) for oversupply ($p<0.001$ for comparison).

4.3.2.5 Persistence

A total of 12,057 and 2,605 episodes of chronic medicine use in the FV and KY databases respectively were assessed for persistence. For the FV database, overall mean time to discontinuation (TTD) was 193 days (95% CI: 188 to 198 days) and median TTD was 92 days (IQR: 50 to 186 days) corresponding to 12% of patients remaining persistent to therapy at one year. Persistence was slightly higher for men than women (median TTD: 100 vs. 87 days, $p=0.001$). In the KY database, the overall mean TTD was 154 days (95% CI: 145 to 163 days) and the overall median TTD was 30 days (IQR: 30 to 142 days) signalling a large drop-off of patients at this time-point. Ten percent of patients overall were persistent with their chronic therapy at one year with no discernible difference between men and women (median TTD: 30 vs. 30 days, $p=0.24$).

Age had a similar effect on persistence as it did on adherence for both databases, with median TTD in the FV databases increasing steadily with age and doubling from 60 days for patients aged 10 to 19 years to 120 days for patients over age 70; over double the percentage of patients remained on therapy at one year between these extremes (7 vs. 18%) (Figure 4.21(a)). For the KY database among age groups, patients 40 years of age and greater had a smaller initial drop-off after which point longer term differences in persistence became apparent (Figure 4.21(b)). Median TTD remained at 30 days for patients aged 0 to 39 years (7% persistent at one year), and peaked at 90 days (IQR: 30 to 270 days) for patients aged 60 to 69 years (18% persistent at one year).

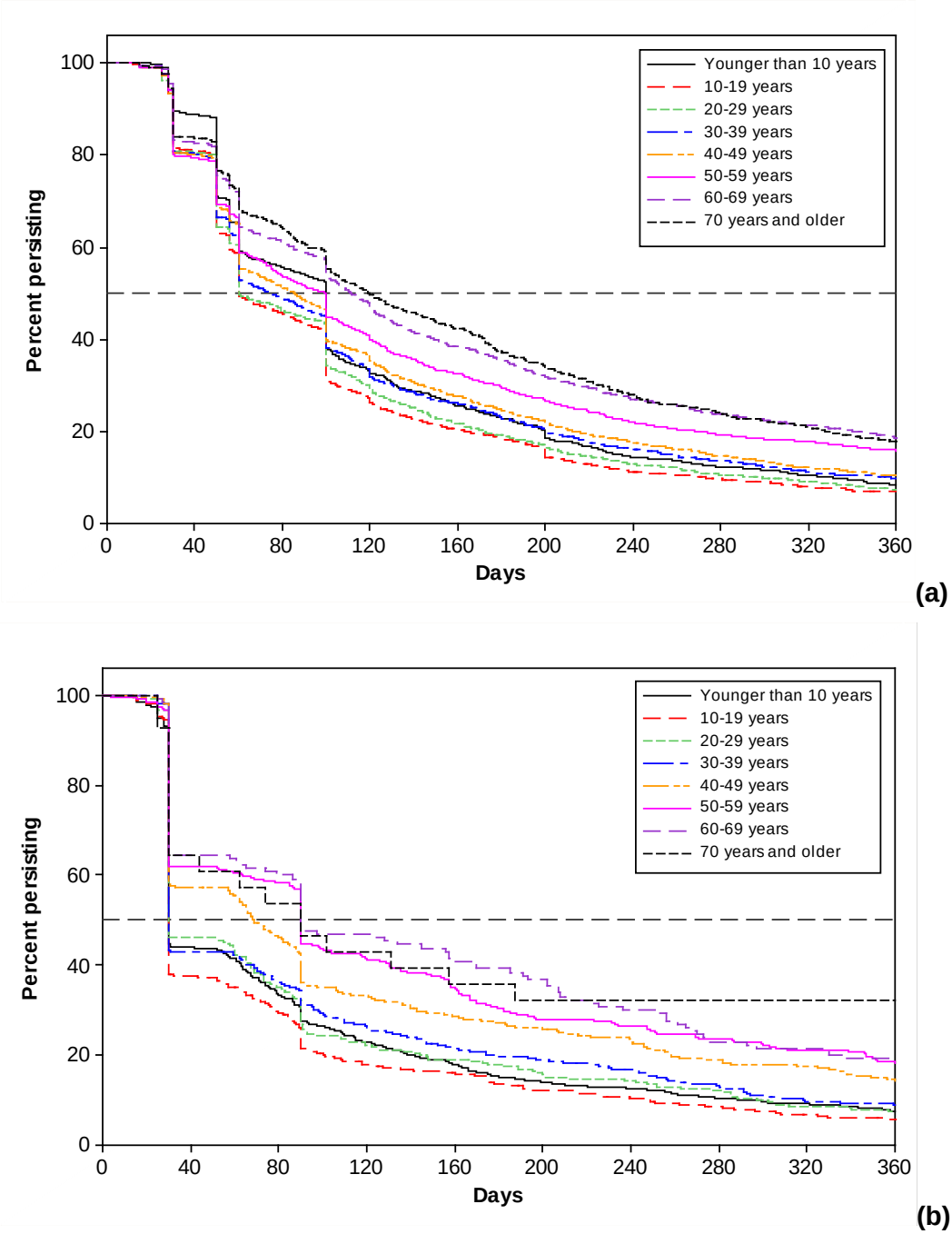


Figure 4.21: Persistence curve for patients with asthma by age (2008) in the **(a)** FV database and **(b)** KY database

In the FV database, theophylline had a significantly higher one-year persistence rate over other therapies at 34%, with a median TTD of 184 days (IQR: 70 to 365 days) (Figure 4.22(a)). Among inhaled therapies, ICS had the highest median TTD at 100 days (IQR: 50 to 207 days), although the persistence dropped off significantly after this point to match the trend of other inhaled therapies. In the KY database, ICS had the lowest persistence at a median TTD of 30 days (IQR: 30 to 77 days) and only

3% of patients remained persistent at one year (Figure 4.22(b)). Median TTD for theophylline and LTRA were higher at 90 days (IQR: 30 to 365 days) and 87 days (IQR: 30 to 251 days), respectively. This corresponded to a one-year persistence rate of 31% for theophylline and 16% for LTRA.

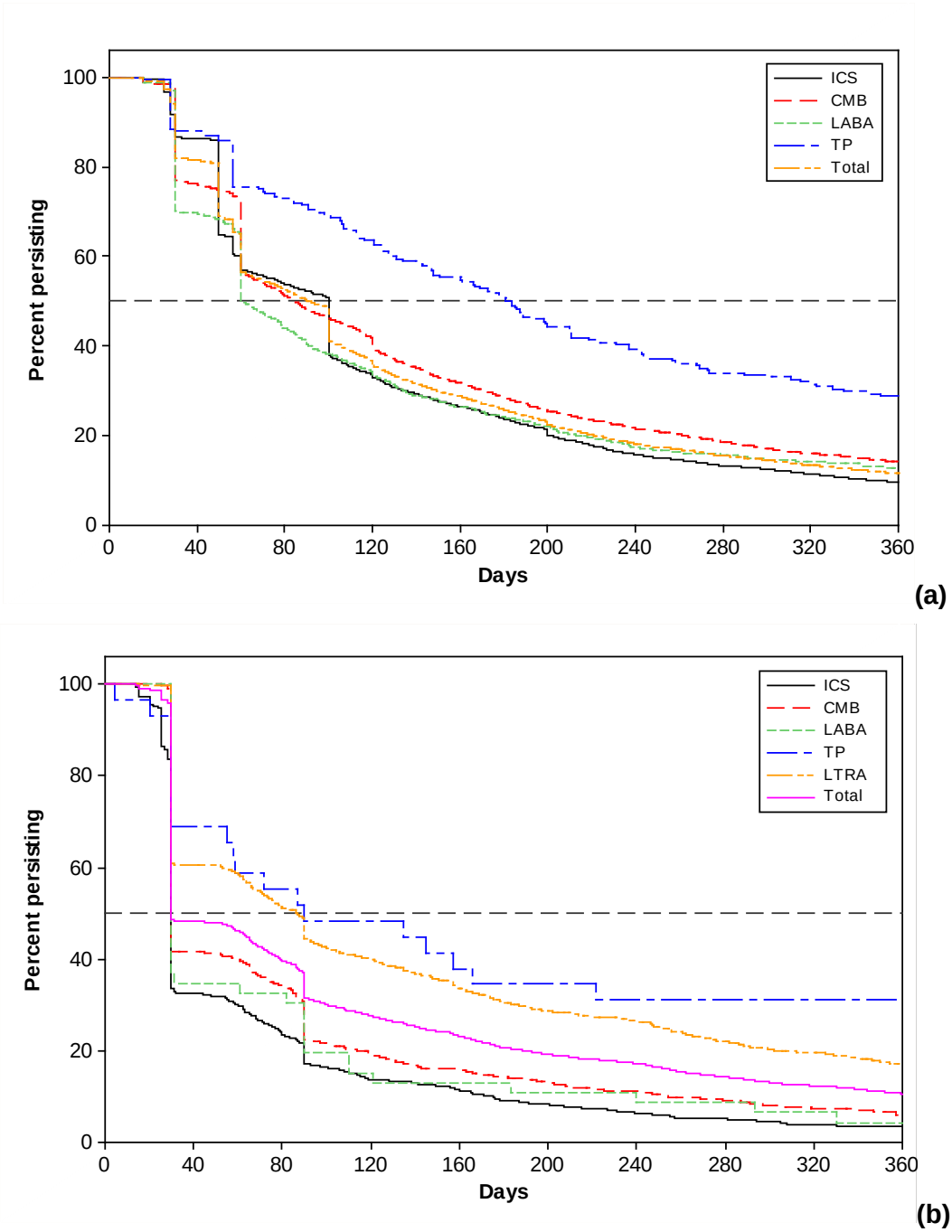


Figure 4.22: Persistence curve for patients with asthma by therapeutic class (2008) in the **(a)** FV database and **(b)** KY database

Adjusting the definition for persistence from 30 days increased the median TTD in the FV database from 92 days and 12% one-year persistence to 112 days and 20% persistence (for a 60-day window), and 156 days and 27% persistence (for a 90-day window). Likewise, the median TTD in the KY database increased from 30 days and 10% one-year persistence to 90 days and 18% persistence (60-day window) and 107 days and 23% persistence (90-day window).

4.3.3 Discussion

Almost all medicines in the FV database sustained decreases in utilisation from 2007 – 2009, including medicines previously found to be increasing in the PIS database analysis for all of Scotland. Among maintenance therapies only the use of Clenil Modulite®, Qvar® and budesonide/formoterol were found to be increasing.

Although budesonide/formoterol was approved for the treatment of asthma initially in 2001, the licensing was updated in 2007 to include the SMART® regimen (Symbicort® inhaler Maintenance And Reliever Therapy). This novel treatment approach allows patients to use a single budesonide/formoterol inhaler as both maintenance and reliever therapy with regular dosing at 2 to 4 puffs daily and an additional 1 puff as needed in response to symptoms. It is included as an option for adult patients at step 3 of the BTS/SIGN guideline (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2012). The introduction of this product at the beginning of the analysis period may explain some of the utilisation increases seen for budesonide/formoterol in the FV database. However, it is likely that other factors also contribute as the SMART® regimen is not approved in the USA and increases in utilisation were also seen in the KY database.

Most of these trends among common medicines were mirrored in the KY database although the magnitude often differed. In both databases the use of OCS also increased significantly. It should be noted that OCS has several therapeutic indications, and use may not reflect treatment for asthma-related exacerbations. However, unlike the PIS database analysis the FV and KY databases limit the patient population using diagnostic data and therefore OCS should theoretically serve as a good but not particularly sensitive proxy for asthma control.

With less utilisation of maintenance medications and increased utilisation of oral steroids, there is question whether asthma may be worsening over time. Asthma prevalence in both Scotland and NHS Forth Valley increased 11.3% and 11.0%, respectively from 2006/07 to 2012/13 (Information Services Division Scotland, 2013b); similarly asthma prevalence in the south region of the USA, which includes Kentucky, increased 13.7% from 2006 – 2010 (Moorman *et al.*, 2012). With increasing prevalence, increased utilisation of maintenance medicine would be anticipated but this is not reflected within this analysis. Examining trend data regarding asthma morbidity and mortality provides further insight. In Scotland, both consultations at GP surgeries and hospital episodes for asthma have held relatively stable in recent years, (Information Services Division Scotland, 2013a; Practice Team Initiative, 2013a) yet the overall rate of death due to asthma decreased by 36% from 2002 – 2012 (General Register Office for Scotland, 2013c). In parallel in the USA, rates of physician office visits, emergency visits and hospitalisations have also held stable, while the asthma death rate has decreased 30% since 2001 (Moorman *et al.*, 2012). This would suggest that despite an increasing prevalence of asthma, outcomes have remained stable. Whether there is room for these measures to improve is a separate issue altogether.

Medication utilisation on the whole was lower among patients in the KY database compared to the FV database, which raises an important point that must be made regarding certain comparisons between the two databases. The FV database was derived from prescribing data at the level of the GP practice and represents prescriptions issued to patients by the GP prior to pharmacy involvement. The KY database, on the other hand, is derived from administrative claims for reimbursement from community pharmacies and therefore only includes prescriptions which have continued through the point of dispensing from the pharmacy to the patient. Prescriptions in the UK are generally written for a limited initial supply and a patient continues therapy by obtaining a new prescription, either by requesting it from the GP or more commonly through a 'managed repeat' service where the pharmacist communicates with the GP for further supply. The GP has general provision over the medication supply, such as the decision to allow early or extra repeat prescriptions at the patient's request. Prescriptions in the USA obtained through third-party insurance, as was the case for the KY database, are written for an initial supply and generally are valid for as many refills as the prescriber indicates

for 12 months after the issue date at which point a new prescription must be written. The timing and quantity of medication supply that the pharmacy dispenses to the patient is largely controlled by the insurance carrier, which may refuse to pay for a medication supply if the patient requests the medication too early before their last supply is due to run out or asks for more than a 30-day supply. The charge of the prescription to the patient is also determined by the carrier based on the patient's individual insurance plan and whether the medication is within the plan's formulary. This can vary from no cost to the wholesale price of the medication to the pharmacy. Infrequently, patients may have dual insurance, such as patients over 65 years old who maintain private insurance while also receiving publicly-funded insurance through Medicare.

This inherent difference in the datasets has the potential to affect several metrics. Figures for DDDs and adherence/persistence in the FV database likely overestimate reality and the comparison to the KY database due to being unable to quantify the rate of primary non-adherence. If the present analysis made a crude adjustment by assuming a liberal gap of 50% between written and collected prescriptions, mean DDD utilisation in the FV database is still over 3-fold higher for SABA, 5-fold higher for total ICS and 1.5-fold higher for combination therapy inhalers than the KY database. In fact, among comparable estimates, only OCS utilisation would be higher in the KY database by a margin of nearly 2-fold. However, if the same adjustment were made for adherence/persistence, the median MPR and median TTD for the FV database become less than or equal to that of the KY database, affecting the overall comparative assessment of prescribing between the two databases.

It should also be noted that several outliers were noted among DDD estimates in the KY database, centred at December 2007. A variety of considerations were given to explaining this anomaly, including policy changes or clinical reasons for a large increase in utilisation. However, the large magnitude, short span and consistency of spike across several medications makes the possibility of a data error more likely. The accuracy of derived figures created by the present researcher was verified, suggesting a likely error on the part of the data source.

The PDD, or average prescribed dose, was calculated for ICS products in both databases. There is no 'correct' ICS dose anticipated from this analysis, but the patterns are useful to first, compare dosing of ICS products and second, to compare dosing strategies internationally. Ideally, doses should be approximately halved for children aged 5 to 12 years old compared to adults/adolescents and halved for ICS with enhanced potency, including Qvar® and products containing fluticasone or mometasone. Interesting trends were apparent. In both databases, fluticasone doses for adults were in line with doses for other ICS, indicating nearly twice the effective dose being prescribed; however, for children, this was not the case and fluticasone doses were appropriately reduced in comparison to other ICS. The data for fluticasone poses a question: is fluticasone utilised uniformly for patients requiring high doses of ICS, or is the enhanced potency of fluticasone not well recognised in clinical practice? Additionally, the analysis found that average doses for adults were generally higher in the FV database, whereas doses for children were higher in the KY database. With largely similar recommended doses of ICS, this may suggest treatment approaches diverging from the guidelines in either country.

In 2002, the MHRA issued a safety warning regarding the use of ICS in children and the risk of adrenal suppression (Medicines and Healthcare products Regulatory Agency, 2002). The warning was prompted by adverse events reported through the Yellow Card Scheme and currently published literature at the time detailing adrenal crises associated particularly with higher than recommended doses of ICS in children (Drake *et al.*, 2002; Todd *et al.*, 2002; Zahra *et al.*, 2002). A significant amount of press was communicated to clinicians across the UK regarding the maximum licensed ICS doses. The case of one death in Lanarkshire in 2001 was particularly sensationalised among several news outlets after a fatal accident inquiry four years later (BBC News, 2005; Herald Scotland, 2005; Mail Online, 2005) and several clinicians based at Yorkhill Children's Hospital in Glasgow were involved in highlighting the safety issue within literature, both before and after it hit mainstream concern (Paton *et al.*, 2006; Todd *et al.*, 1996). The national safety alerts as well as the local news attention in Scotland are likely to have influenced a more cautious approach in ICS dosing among children in the FV database. While the prescribing information for ICS products in the USA contains safety information regarding adrenal suppression, the media response and safety warnings did not happen to

nearly the same degree and may explain the comparatively higher doses seen in the KY database.

Adherence and persistence with medicine is a key consideration in any analysis regarding medication utilisation. While the WHO estimates that approximately 50% of patients across the world are non-adherent with therapy for chronic disease (World Health Organization, 2003), respiratory disease presents several additional and unique barriers including patient dislike of inhaled formulations, improper inhaler technique and need for alternate unfavourable equipment such as spacers (Restrepo *et al.*, 2008). Not surprisingly, adherence with asthma therapy has been shown to be as low as 30% (Bender *et al.*, 1997), and has been thought to contribute significantly to the presence of severe refractory disease (Gamble *et al.*, 2009).

Primary non-adherence, or failing to redeem a prescription at the pharmacy, has not been widely quantified in the literature, but estimated rates in two systematic reviews varied widely from 0.5 to over 50% (Gadkari *et al.*, 2010; Zeber *et al.*, 2013). These figures may also vary according to therapeutic class and indication; one analysis found a nearly 20% differential between primary non-adherence rates between medicines for osteoporosis and infection (Shin *et al.*, 2012). The treatment of asthma may be particularly vulnerable to primary non-adherence, as two recent Canadian analyses found that only 62.4% and 52.6% of the prescribed supplies of inhaled corticosteroids were then dispensed to children and adults with asthma, respectively (Blais *et al.*, 2011; Pando *et al.*, 2010). However, how this data applies to clinical practice within the UK and USA is difficult to assess, as the gap between prescribing and dispensing has also been found to vary according to whether the patient receives their medication under a privately- or publicly-funded payment model (Cyr *et al.*, 2013). More specifically, cost to the patient has been widely shown to have a negative effect on medication adherence, both for medications at-large (Eaddy *et al.*, 2012), and respiratory medications in particular (Vaidya *et al.*, 2013) – a concern disproportionately affecting patients in the KY database.

Although now free of charge, prior to April 2011, prescriptions in NHS Scotland were dispensed with a flat charge of £4.00 to £5.00 per prescription. Full exemptions were given to patients under 18 or over 60 years of age, those with selected co-

morbidities and those on publicly-funded benefit schemes. Prescriptions in the USA processed through third-party payers are subject to varying levels of cost-share to the patient, much of which may be significant for the patient. A study in the USA quantified older patients' perceptions of medications as a function of importance and worth; among 12 therapeutic classes assessed, medications for asthma/allergy were rated with the second lowest importance, third highest expense, and fourth lowest overall worth (Lau *et al.*, 2008). A significant association was found for perceived importance and worth with this relationship stronger among expensive medications compared to inexpensive medications (Lau *et al.*, 2008).

A number of analyses have found that some patients do not believe maintenance medications to be useful for their disease or do not believe that their disease is severe enough to require them, regardless of whether their assessment is correct or not (Howell, 2008). What appears to be most important is the patient's perception of the medication and if it improves potentially distressing symptoms of disease. Patients who actually do have less severe or persistent asthma also tend to have lower adherence as the perceived benefits of treatment are lower (Williams *et al.*, 2007); this may be particularly prevalent for patients that have seasonal symptom patterns or symptoms that are induced by factors such as allergens or exercise. Also, if a patient has a negative view of their disease and expects their symptoms to be a normal daily occurrence, they may not choose to use their therapy until they feel very unwell. Lastly, the presence of adverse effects – or simply the perceived potential for them – also leads patients to have poor adherence by decreasing the 'return on investment' of taking their medicine (Canonica *et al.*, 2007).

Approximately one-half of episodes in the FV database and one-quarter of episodes in the KY database provided a medication supply of at least 80%. These figures are mainly interpreted in tandem rather than in comparison, due to inherent differences between the FV and KY databases described previously. Although these differences potentially affect any comparison of the two databases they are particularly pertinent within the realm of adherence and persistence. Nonetheless, it is evident that adherence to asthma therapy is poor. Several other analyses have evaluated adherence to respiratory medicine often without regard to diagnosis (including both patients with asthma and COPD) and have found adherence rates similar to the present analysis. Several studies evaluating adherence and persistence have been

conducted in Sweden using pharmacy record databases; among these for respiratory medications, it was found that satisfactory refills occurred in only 28 to 35% of cases and that undersupply ranged from 42 to 59% (Krigsman, Moen*, et al.*, 2007; Krigsman, Nilsson*, et al.*, 2007). A recent Scottish study also evaluated adherence specifically in children with asthma and found that only 15 to 39% of patients achieved an adequate MPR with maintenance medication; this study further correlated MPR with use of SABA/OCS and found that use of these therapies was more common among patients with adequate adherence (Elkout *et al.*, 2012).

This unusual finding was replicated in the current analysis. It may have been expected that a high use of reliever therapy should correspond with poor adherence to maintenance therapy as it is thought that symptomatic patients may have a poorer sense of control and ownership over their illness resulting in lower motivation and overall medication adherence (Horne *et al.*, 1999). This would be supported by the increasing utilisation trend found for OCS, coupled with the low rates of adherence/persistence with maintenance medication. A patient may feel immediate benefit with the use of their SABA inhaler or a course of OCS, but fail to feel the same benefit with their maintenance inhaler and therefore not take it. However, the direction of causation in the relationship between reliever and maintenance therapy is unclear, as patients who are symptomatic with increased use of reliever therapy also may be inclined to develop better adherence to their controller therapy. This is particularly the case where the patient perceives the medication as a necessity and therefore has greater incentive toward continued therapy (Kucukarslan, 2012). It is clear that the relationship between reliever and maintenance therapy is multifactorial and subject to many individual patient considerations that may not be clear in a population-based analysis.

Persistence is a measure of long-term adherence to medication, and is a useful metric for chronic diseases where therapy is expected to be long-term or life-long. For patients on maintenance treatment for asthma, it would be expected that their disease was chronic enough to require long-term therapy and therefore persistence would be an appropriate measure. However, the rates of persistence were found to be low with only 12% of patients in the FV database and 10% of patients in the KY database remaining persistent at one-year. This was similar to other analyses, including a Swedish analysis where only 13% of patients received enough ICS or

combination inhalers to supply at least 1 DDD/day over the treatment period (Haupt *et al.*, 2008). Further analyses have estimated one-year persistence rates at 10% (Marceau *et al.*, 2006) and 18% (Breekveldt-Postma *et al.*, 2004). However, these figures should be considered with several factors in mind. First, persistence calculations are sensitive to how stringent the definition is set. For the present analysis, a repeat prescription gap of 30 days was utilised, although this was varied to 60 and 90 days, with the one-year persistence rate nearly doubling with this adjustment. Secondly, the calculation also was only able to gauge persistence for a single therapeutic class at any given time and therefore major therapy changes (such as from ICS alone to a combination therapy inhaler) would result in two persistence calculations. For asthma, where patients may require long-term therapy, but have that therapy changed relatively frequently, persistence may present a 'worst-case scenario' view of medicine-taking behaviours. It should also be noted that the persistence analysis included patients who were on both prevalent and new therapies at the beginning of the analysis window. Because of the short time frame of data availability, there was no 'run-in' period, and patients may have received a therapy prior to the persistence analysis, and only had the last year of their medicine-taking behaviour captured. This has the ability to affect the results by inflating persistence rates, as patients on prevalent therapy at the beginning of the analysis are more likely to continue taking their medicine, unlike patients on new therapy, who are less established in their routine and more likely to drop off. Lastly, the size of available inhalers is to be expected to influence the calculations. For instance, in the FV database, drop offs in the Kaplan-Meier curves are evident at 60 and 100 days, corresponding to 60/120-dose and 200-dose inhaler sizes, respectively. These drop offs represent the patients who received only one prescription but the number of days they were considered persistent was entirely due to the type of inhaler they received.

Medicines administered by the oral route (theophylline in both databases, and LTRA in the KY database) were associated with the best adherence and persistence across all maintenance medications. Adherence is known to decrease as the dosing frequency of a medication increases (Coleman *et al.*, 2012) which may explain preference for a once-daily regimen with an LTRA. However, as theophyllines are dosed twice daily as many of the inhaled therapies for asthma, there is likely some additional influence of patient preference for oral therapies over inhaled therapies.

Patients may find inhalers difficult to use, socially unacceptable in public places or with disagreeable taste on dosing and may be less inclined to be adherent.

Age also appeared to correlate positively with adherence and persistence. The low MPR and TTD among younger patients may be explained by several factors. Children may be more likely to present with wheezy illness which may be diagnosed and treated similarly to asthma albeit on a more intermittent basis. However, this is more likely to result in the use of SABA as opposed to the maintenance medications assessed in the adherence and persistence analyses. Children and adolescents also have the influence of their parents in their therapy which may play a role. Education levels, socio-demographic characteristics, and the balance of necessity and concern for treatment among parents have been linked to their children's adherence with asthma therapy, and ultimately the risk of uncontrolled asthma (Conn *et al.*, 2007; Koster *et al.*, 2011). In both databases, adherence and persistence was higher among younger children (less than 10 years old) compared to adolescents (10 to 19 year olds), which may represent the effect of transition to adulthood where younger patients take more control over their medical decisions, including whether to take their therapy as prescribed.

In 2014, the results of the National Review of Asthma Deaths were published. The report provided a detailed account of 195 deaths in the UK thought to be related to asthma from February 2012 – January 2013 (Royal College of Physicians, 2014). Among these deaths, 57% of patients had no record of specialist care and 43% had no record of an asthma review by their GP in the year before their death (Royal College of Physicians, 2014). There was evidence of significant under-prescribing, with 80% of patients receiving fewer than 12 maintenance inhalers and 38% of patients receiving fewer than four maintenance inhalers in the year prior to their death (Royal College of Physicians, 2014). Recommendations from this report emphasised the dangers associated with non-adherence and the need for better prescribing to improve asthma care. The findings from within NHS Forth Valley demonstrate a similar lack of adherence. Although death from asthma is relatively rare, it is preventable and focusing on medication adherence, as recommended in the review, is an important move toward quality improvement in the clinical care of asthma.

4.4 Treatment investigations

4.4.1 Methods

Step stratification

Patients with asthma in the FV and KY databases who received treatment during 2008 were also classified according to the BTS/SIGN asthma guideline step classification (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2012). Each patient's therapy during the year was determined and assigned to a step within the guideline. Due to the ambiguity in the definition of step 2/3, two interpretations of the guideline were examined (Table 4.7). The first interpretation (BTS/SIGN (a)) was a literal interpretation of the guideline and defined step 2 to include both low- and medium-dose ICS, with step 3 defined as low- and medium-dose combination therapy. For the second interpretation (BTS/SIGN (b)), only low-dose ICS was considered within step 2 and medium-dose ICS was considered to be step 3 along with low- and medium-dose combination therapy.

Table 4.7: BTS/SIGN guideline interpretation
For adults/adolescents: low-dose = 0-400 mcg daily; medium-dose > 400-800 mcg daily; high-dose > 800 mcg daily (BDP-equivalent)

Step	BTS/SIGN (a)	BTS/SIGN (b)
5	Oral corticosteroids of >14 day supply with no titration schedule	
4	High-dose ICS alone High-dose ICS + LABA/TP/LTRA High-dose ICS + TP	
3	Low-/medium-dose ICS + LABA Low-/medium-dose ICS + TP/LTRA	Medium-dose ICS alone Low-/medium-dose ICS + LABA Low-/medium-dose ICS + TP/LTRA
2	Low-/medium-dose ICS alone TP/LTRA alone	Low-dose ICS alone TP/LTRA alone
1	Inhaled SABA only	

The asthma step classification was assessed for patients in both the FV and KY databases and separately for adults/adolescents and children. Dose cut-offs for children were halved compared to adults/adolescents, as recommended in the BTS/SIGN guideline. Data queries were run in ascending step order with inclusion and exclusion criteria for the therapy prescribed and were designed to capture patients who were prescribed one regimen while excluding prescribing of all

regimens in higher steps (queries 19 – 28). Patients meeting criteria for two sequential asthma steps during the year studied were assumed to have 'stepped up' and were classified into the higher step. Inhaled SABA therapy was permitted at all steps as was the intermittent use of short-term oral corticosteroids defined as a course of less than 14 days duration or with a titrating schedule. Therapy at step 3 was further stratified (using the BTS/SIGN (b)) interpretation) to examine the prevalence of different therapy choices. Patient and clinical characteristics were assessed according to step classification for both databases, including age, sex, presence of co-morbid COPD, and utilisation of SABA and OCS during 2008. Smoking status was also assessed but only for the FV database, as this information was unavailable in the KY database.

Initiation of combination inhaler therapy

Therapy transitions at initiation of combination therapy inhalers were also analysed. Patients with asthma in the FV and KY databases were included if they received their first prescription for a combination therapy inhaler in 2008 or 2009 (considered their 'index date'); they also had to have at least six months of prescription history prior to the index date to assess their previous therapy (queries 29 – 30). The analysis investigated patients who were naïve to combination therapy and therefore excluded patients who had received a LABA in the year prior to the index date. Two sensitivity analyses were performed: one separately assessing patients who had received a LABA in the previous year and one excluding patients with a co-morbid diagnosis of COPD from the original full analysis.

Dose changes at the index date were assessed in continuous form using a paired t-test and then further assessed according to dose categories for the dose of ICS therapy they received pre-index date and the dose of ICS in the combination therapy they received on the index date. The pre-index ICS dose used was the highest dose prescribed in the year before while the combination therapy inhaler dose used was the prescribed dose on the index date. Doses were standardised to BDP equivalent and classified as low-, medium- or high-dose as appropriate for whether the patient was an adult/adolescent or child. The use of SABA and OCS in the year prior to the index date was quantified as markers of asthma symptoms and exacerbations, respectively.

Clinician survey of BTS/SIGN guideline

Based on the results of the step therapy and PDD analyses, an electronic survey questionnaire was created to assess opinions and understanding of the BTS/SIGN asthma guideline from the clinician perspective. The survey was designed using Qualtrics® survey software (Qualtrics; Provo, UT) and contained 10 core questions, including three case vignettes with six associated questions regarding step classification and four multiple-response questions on ICS dose equivalencies (Appendix IV). Questions were asked using proprietary names based on perceived familiarity of clinicians with these specific products; UK proprietary names utilised in the questionnaire included Clenil Modulite® (HFA-BDP), Qvar® (extra fine HFA-BDP), Flixotide® (fluticasone), Asmanex® (mometasone), Seretide® (fluticasone/salmeterol), Symbicort® (budesonide/formoterol) and Serevent® (salmeterol).

Each case assessed understanding of the guideline step scheme by asking the clinician to classify the step of therapy the patient was receiving (questions 1.1, 2.1 and 3.1); while the first two questions had straightforward answers, the ICS in question three was purposely assigned within the step 2/3 ambiguity within the BTS/SIGN guideline. Case 1 was further designed to assess the preference of the clinician regarding choosing between escalation from low- to medium-dose ICS therapy or transition to low-dose combination inhaler therapy. Case 2 presented a patient post-exacerbation to assess whether the historical preference of ICS dose increase was still employed in this situation. Case 3 displayed a patient who would be considered at a good level of control within the current guidelines to determine whether clinicians agreed with this assessment and if they chose to 'step-down' or continue current therapy. For the multiple response questions, clinicians were asked to identify equivalent doses from various ICS regimens with each question possibly having more than one correct answer. Expected answers were derived from equivalencies in the BTS/SIGN guideline, which standardise all products to BDP, with BDP extra fine HFA-BDP, fluticasone and mometasone considered twice as potent as BDP and budesonide.

Surveys were sent out to GPs, practice managers and practice nurses in the 57 practices within the NHS Forth Valley Health Board via email. The exact number of survey recipients was unable to be pinpointed as a general email listserv was utilised, although the listserv included individuals at all practices in the health board.

No similar email list was available for pharmacists within the health board, however, contact with the Royal Pharmaceutical Society (RPS) enabled a separate notification to be sent out to pharmacists through the RPS network; notably, this listserv was not specific to NHS Forth Valley bur rather included RPS-member pharmacists across Scotland. Recipients received text explaining the goals of the survey and information regarding participation, and an electronic link to the survey if they wished to participate. The ten core survey questions were presented in randomised block format (blocks for the two types of questions, but randomised within), followed by a short series of general demographic information, including (1) current profession, (2) length registered or in active practice, (3) frequency of involvement in the care of asthma patients and (4) frequency of utilisation of the BTS/SIGN guideline in clinical practice, and for the survey. All responses were anonymous from the point of collection and a respondent was allowed to leave questions blank if they desired. The initial survey was released 25 June 2013, with follow-up emails sent out on 9 July 2013 and 23 July 2013; the survey closed to further data collection on 6 August 2013. Surveys that were started were either completed by the respondent submitting the survey themselves, the software automatically closing out their survey after 4 weeks from their initial login or with the end of the collection period. Results were descriptively analysed as a full cohort, and stratified by professional status of the respondent (GP, nurse or pharmacist). For the multiple-response ICS equivalency questions (where the delineation between correct/incorrect answers was clear), an overall percentage score (and SEM) was calculated, and compared among professions using a one-way ANOVA test and Tukey's inter-group comparison.

4.4.2 Results

4.4.2.1 Step stratification

A total of 12,319 adult and adolescent patients with asthma had therapy recorded in the FV database during 2008. The step classification for the BTS/SIGN (a) interpretation was 1,957 (15.9%), 3,911 (31.7%), 1,856 (15.1%), 3,978 (32.3%) and 149 (1.2%) patients for steps 1 to 5, respectively. Four hundred and sixty-eight patients (3.8%) received therapy combinations outside the guideline recommendations and were unable to be classified. Altering the step 2/3 definitions to BTS/SIGN (b) resulted in shift of 1,145 (9.2%) of patients from step 2 to step 3 representing those patients who received medium-dose ICS therapy alone. At step 3, medium-dose ICS alone was the preferred therapy (1,145 patients; 38.1% of step) above low-dose combination therapy (979 patients; 32.6% of step) and medium-dose combination therapy (806 patients; 26.8% of step). ICS therapy in combination with theophyllines made up the small number of remaining patients.

In the KY database, 2,512 patients with asthma received therapy during 2008, resulting in a BTS/SIGN (a) step classification of 757 (30.1%), 551 (21.9%), 250 (10.0%), 710 (28.3%) and 129 (5.1%) patients for steps 1 to 5, respectively. A total of 115 (4.6%) patients received therapy unable to be classified using the guideline. Using the BTS/SIGN (b) guideline resulted in 48 (1.9%) patients who received medium-dose ICS shifting within the classification scheme. The preferred therapy at step 3 was low-dose combination therapy with 154 (51.7% of step) patients, followed by medium-dose ICS alone (48 patients; 16.1% of step), medium-dose combination therapy (46 patients; 15.4% of step) and ICS in combination with TP/LTRA (46 patients; 15.4%).

Comparison of the FV and KY databases showed differences in the step classifications (Figure 4.23). Nearly twice as many patients in the KY database were classified at step 1 compared to the FV database; the number of patients in the KY database at step 5 was nearly five-fold more than in the FV database which had more patients at steps 2 to 4.

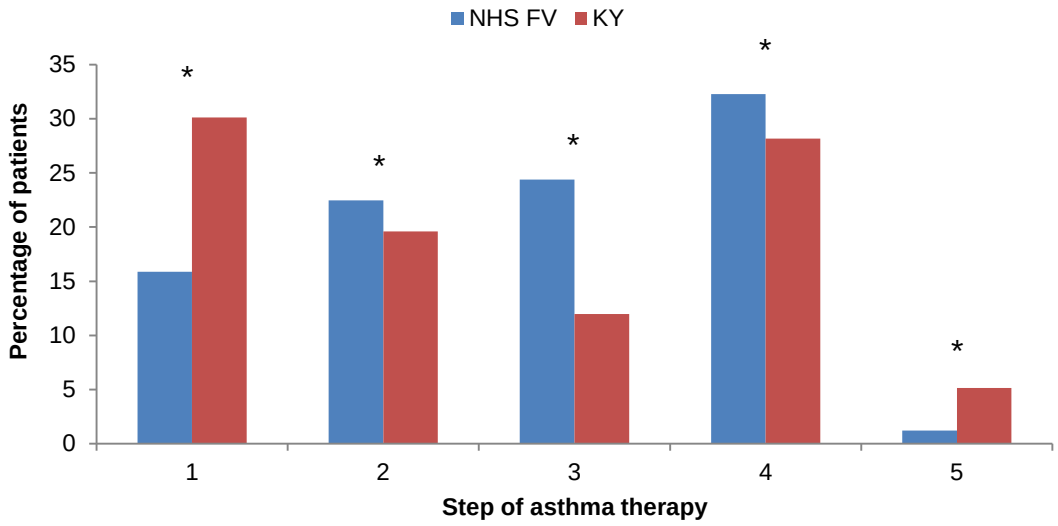


Figure 4.23: Comparison of asthma step classification for adults/adolescents in the FV and KY databases using the BTS/SIGN (b) interpretation (2008)
** p<0.05 for comparison between guidelines*

For the FV database, 1,401 children aged 5 to 12 years old received therapy and were classified with a BTS/SIGN (a) stratification of 244 (17.4%), 827 (59.0%), 185 (13.2%), 102 (7.3%) and 3 (0.2%) patients in steps 1 to 5, respectively; 40 (2.9%) patients were unable to be classified. Using the BTS/SIGN (b) interpretation resulted in shift of 297 (21.2%) patients who received medium-dose ICS alone, which was the most common therapy utilised at step 3 (61.4% of step). Other therapies included medium-dose combination therapy (131 patients; 27.1% of step) and low-dose combination therapy (47 patients; 9.7% of step).

A total of 612 children received therapy in the KY database. Using the BTS/SIGN (a) classification, there were 144 (23.5%), 219 (35.8%), 54 (8.8%), 165 (27.0%) and 2 (0.3%) patients in steps 1 to 5 respectively. Twenty eight (4.6%) patients received therapy outside guideline recommendations. The BTS/SIGN (b) classification moved 34 (5.6%) patients from step 2 to 3 who received medium-dose ICS alone (38.6% of step). The most common therapy was ICS in combination with TP/LTRA (37 patients; 42.0% of step); 17 (19.3% of step) patients received medium-dose combination therapy and no patients received low-dose combination therapy.

For the comparison between the FV and KY databases, the KY database had more children classified at steps 1 and 4 and the FV database had more patients classified at steps 2 and 3 (Figure 4.24). The imbalance at later steps was particularly significant, with a two-fold differential at step 3 and a four-fold differential at step 4.

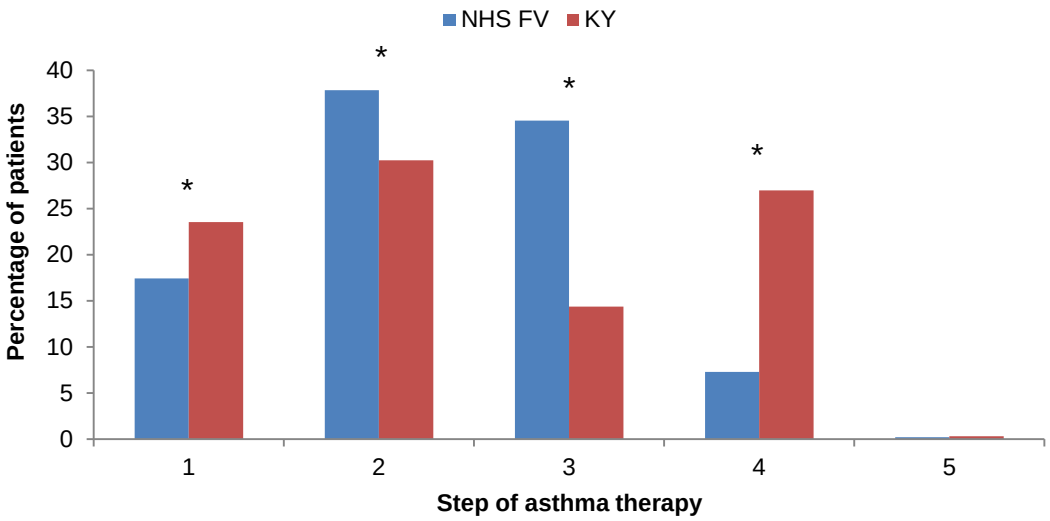


Figure 4.24: Comparison of asthma step classification for children in the FV and KY databases using the BTS/SIGN (b) interpretation (2008)
** p<0.05 for comparison between guidelines*

In the FV database, the prevalence of women increased by nearly 10% from step 1 to step 5; increases in the median age and proportion of patients with co-morbid COPD were also evident (Table 4.8(a)). In the KY database, women similarly made up the majority of patients although no pattern was apparent with stepwise classification. Increases in median age and proportion of co-morbid COPD were present although slightly more erratic (Table 4.8(b)). The percentage of patients who received a SABA with their step therapy was higher within the FV database, while the percentage of patients with an OCS was higher in the KY database. For both databases the doses of SABA and courses of OCS increased as step increased.

Table 4.8a: Patient/clinical characteristics within asthma adult step classification using the BTS/SIGN (b) interpretation (2008) in the FV database

Characteristic	Total	Step				
		1	2	3	4	5
Female, n (%)	7,226 (58.7)	1,039 (53.1)	1,595 (57.7)	1,816 (60.5)	2,412 (60.6)	93 (62.4)
Median age (IQR)	44 (30-60)	36 (23-48	40 (23-55)	44 (31-59)	51 (38-64)	65 (50-73)
COPD, n (%)	849 (6.9)	86 (4.4)	57 (2.1)	120 (4.0)	511 (12.8)	37 (24.8)
Current smoker, n (%)	2,526 (20.5)	450 (23.0)	506 (18.3)	588 (19.6)	860 (21.6)	33 (22.1)
SABA, n (%)	10,825 (87.9)	1,957 (100.0)	2,508 (90.7)	2,618 (87.2)	3,606 (90.6)	136 (91.3)
Doses/day, median (IQR)	1.9 (1.1-4.4)	1.1 (0.6-2.2)	1.6 (0.8-3.3)	1.6 (1.1-3.8)	2.7 (1.1-5.5)	4.3 (1.6-7.7)
OCS, n (%)	2,372 (19.3)	98 (5.0)	305 (11.0)	477 (15.9)	1,090 (27.4)	149 (100.0)
Courses, mean (SEM)	2.4 (0.06)	1.6 (0.14)	1.4 (0.05)	1.7 (0.06)	2.3 (0.07)	7.4 (0.4)

Table 4.8b: Patient/clinical characteristics within asthma adult step classification using the BTS/SIGN (b) interpretation (2008) in the KY database

Characteristic	Total	Step				
		1	2	3	4	5
Female, n (%)	1,555 (61.9)	478 (63.1)	327 (65.0)	196 (65.8)	413 (58.2)	80 (62.0)
Median age (IQR)	42 (28-54)	38 (25-49)	40 (25-53)	45 (32-57)	44 (32-55)	49 (37-61)
COPD, n (%)	391 (15.6)	84 (17.6)	56 (17.1)	43 (14.4)	142 (20.0)	53 (41.1)
SABA, n (%)	1,571 (62.5)	757 (100.0)	185 (36.8)	143 (47.9)	336 (47.3)	87 (67.4)
Doses/day, median (IQR)	0.5 (0.5-2.0)	0.5 (0.5-2.0)	0.5 (0.5-2.0)	1.6 (0.5-2.0)	1.6 (0.5-2.2)	2.0 (0.5-2.9)
OCS, n (%)	913 (36.3)	280 (37.0)	143 (28.4)	94 (31.5)	226 (31.8)	129 (100.0)
Courses, mean (SEM)	1.8 (0.08)	1.2 (0.04)	1.4 (0.07)	1.4 (0.09)	1.5 (0.1)	3.4 (0.3)

4.4.2.2 Initiation of combination inhaler therapy

From 2008 – 2009, 685 patients in the FV database and 283 patients in the KY database who were LABA-naïve received their first prescription for a combination therapy inhaler. A small proportion of patients (17; 2.5%) in the FV database had unclear prescription instructions and the dose of their ICS and/or combination therapy was unable to be determined; all patients in the KY database had complete data. A significantly greater proportion of patients in the FV database had received an ICS in the year prior at 541 (79.0%) patients compared to 54 (19.1%) patients in the KY database ($p<0.001$).

For patients with previous ICS treatment the mean standardised dose of ICS before the index date in the FV database was 677 micrograms compared to 1,043 micrograms on initiation of combination inhaler therapy, resulting in a mean increase in ICS dose of 354 micrograms (95% CI: 302 to 407 micrograms, $p<0.001$). Patients originally on low- and medium-dose ICS had mean dose increases of 550 micrograms (95% CI: 483 to 618 micrograms) and 275 micrograms (95% CI: 186 to 363 micrograms), respectively (both $p<0.001$). Patients originally on high-dose ICS had similar doses pre- and post-index (mean difference: 21 micrograms, 95% CI: -97 to 139 micrograms, $p=0.723$). In the KY database, the mean standardised dose of ICS pre-index and combination inhaler therapy post-index was 789 micrograms and 632 micrograms, respectively, with a mean decrease of 157 micrograms (95% CI: 20.6 to 294 micrograms, $p=0.025$). Patients originally on low-dose ICS had a mean dose increase of 293 micrograms (95% CI: 143 to 443 micrograms, $p=0.001$) but patients on medium- and high-dose ICS had an overall decrease in their dose on transition to combination therapy at 138 micrograms (95% CI: 11 to 265 micrograms, $p=0.035$) and 492 micrograms (95% CI: 230 to 754 micrograms, $p=0.001$), respectively.

In the FV database, patients previously on low-, medium- and high-dose ICS were changed to high-dose combination therapy inhalers in 122/250 (48.8% of ICS category; 17.8% of total), 94/151 (62.3%; 13.7%) and 85/113 (75.2%; 12.4%) cases, respectively (Figure 4.25(a)). For patients with no history of previous ICS therapy, 81/144 (56.3%; 11.8%) patients were changed to high-dose combination therapy inhalers. Fifty two (10.3% of those with pre-index ICS) patients were transitioned to

a combination therapy inhaler with a lower dose of ICS than originally. In the KY database, 3/14 (21.4% of ICS category; 1.1% of total), 3/20 (15.0%; 1.1%) and 6/20 (30.0%; 2.1%) patients were changed from low-, medium- and high-dose ICS to high-dose combination therapy inhalers, respectively (Figure 4.25(b)). Patients with no previous ICS therapy represented the majority of patients with 117/229 patients (51.1%; 41.3%) changed to high-dose combination therapy inhalers. Twenty three (42.6%) patients received a lower dose of ICS in their combination therapy inhaler than their previous ICS inhaler.

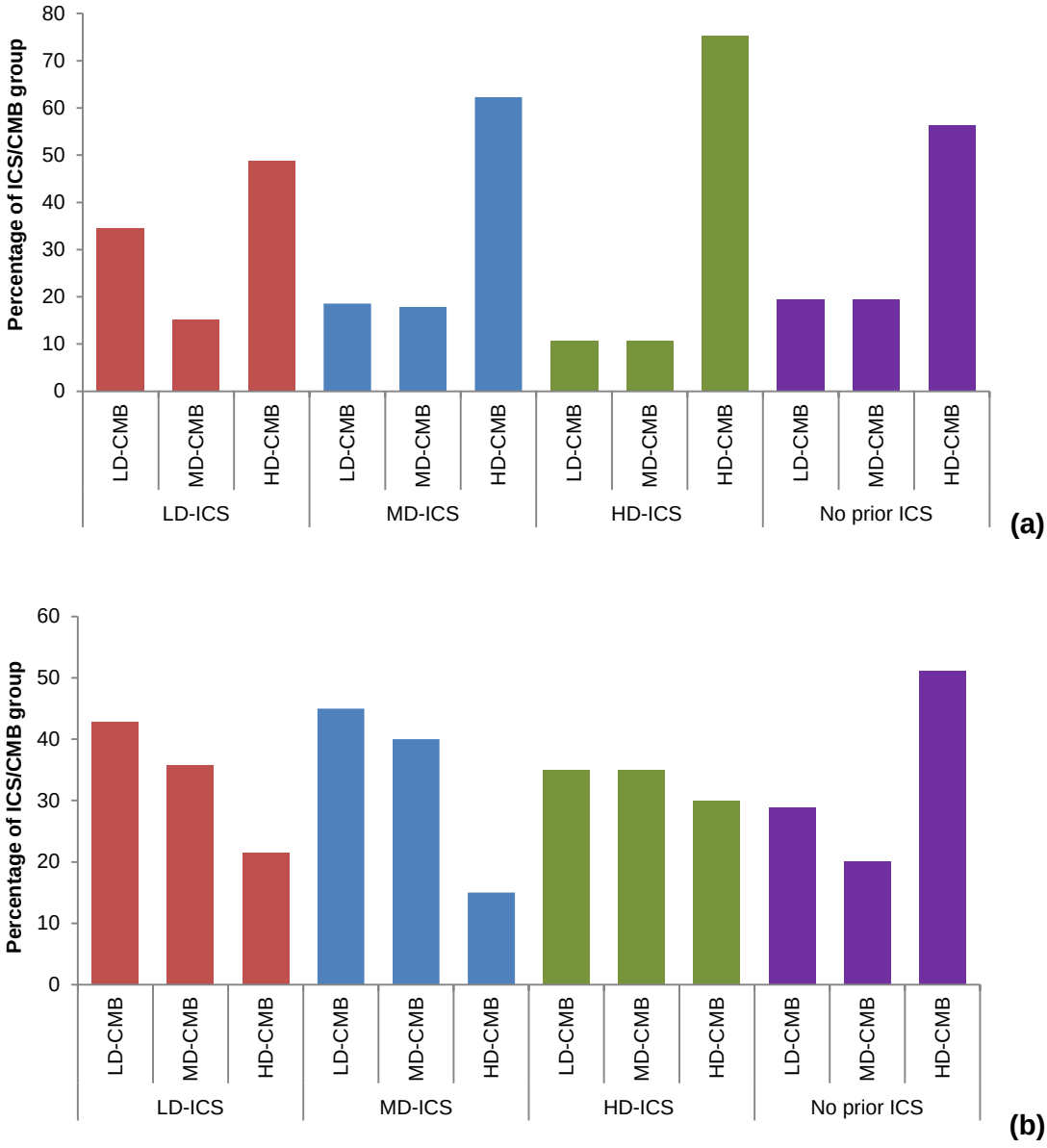


Figure 4.25: Change in dose from ICS to first combination therapy inhaler in the **(a)** FV database and **(b)** KY database (2008 – 2009)

Eighty-nine (13.0%) patients in the FV database and 75 (26.5%) patients in the KY database had concurrent diagnoses of COPD and were included in the original analysis. Excluding these patients from the analysis resulted in a larger increase in ICS dose at the index date (mean difference: 463 micrograms, 95% CI: 406 to 520 micrograms, p<0.001) for the FV database; in the KY database, whereas the dose originally decreased at the index date when COPD patients were excluded from the analysis the difference in ICS dose was no longer statistically significant (mean difference: 125 micrograms, 95% CI: 23 to -273 micrograms, p=0.095).

A further 230 patients in the FV database and 15 patients in the KY database received a LABA in the year prior to initiating therapy with a combination inhaler; 220 patients (95.6%) and 8 patients (53.3%) had also received an ICS (p<0.001 for comparison) indicating previous treatment with combination therapy albeit in separate inhalers. Among these patients in the FV database, the mean standardised doses of ICS and combination inhaler therapy were higher than the original cohort at 1,054 micrograms and 1,220 micrograms, respectively, marked by an overall increase of dose at the index date of 166 micrograms (95% CI: 51 to 281 micrograms, p=0.005). For the KY database, the mean dose pre- and post-index was also higher at 1,090 micrograms and 980 micrograms, respectively, although statistically similar to each other (mean difference: -110 micrograms, 95% CI: -768 to 548 micrograms, p=0.704).

4.4.2.3 Clinician survey on BTS/SIGN guideline

A total of 97 individuals opened the survey and 44 surveys (45.4%) were actively submitted by respondents. Among 41 respondents who provided demographic information, 16 (39.0%) were GPs, 17 (41.4%) were practice nurses, and 8 (19.5%) were pharmacists. All pharmacists were from outside the NHS Forth Valley Health Board. The large majority of respondents (31/41; 75.6%) had been registered or in active practice for more than 10 years and were involved in treating patients with asthma on at least a weekly or daily basis. More nurses (15/17 respondents; 88.2% of group) and pharmacists (6/7 respondents; 85.7% of group) were involved in asthma care at this frequency than GPs (10/16 respondents; 62.5% of group). The majority of respondents (27/41; 65.9%) reported regular consultation of the

BTS/SIGN asthma guideline with the remainder (14/41; 34.1%) reporting only rare use.

Among step classification questions, responses were relatively consistent with expected answers (Table 4.9). For questions 1.1 and 2.1, the majority of respondents classified 400 micrograms BDP-equivalent daily correctly at step 2 at 97.5% and 89.5%, respectively. When cross-tabulated with respondent profession, correct response rates were similar, at 94.1 to 100.0% for question 1.1 and 76.9 to 100.0% for question 2.1. For question 3.1, (where the expected answer was split according to perceived ambiguity in the BTS/SIGN guideline) one-quarter of patients chose step 3 as their response corresponding to a dose of 500 micrograms of BDP-equivalent daily. GPs were most likely to choose step 2 (11/13 respondents; 84.6% of group), followed by nurses (11/15 respondents; 73.3% of group) and lastly, pharmacists (5/8 respondents; 62.5% of group).

Table 4.9: Clinician survey responses (case-based)
Expected responses highlighted

Question and ICS in question	Response	n (%)
1.1 – Clenil Modulite® 200 mcg 1 puff BD	Step 1	1 (2.5)
	Step 2	39 (97.5)
2.1 – Budesonide 200 mcg 1 puff BD	Step 2	34 (89.5)
	Step 3	2 (5.3)
	Step 4	1 (2.6)
	Step 5	1 (2.6)
3.1 – Flixotide Evohaler® 125 mcg 1 puff BD	Step 2	27 (75.0)
	Step 3	9 (25.0)

For case 1, the patient should have been identified with poorly controlled asthma, and either changed to a higher dose of Clenil Modulite® (800 micrograms BDP-equivalent daily) or had a LABA added to therapy by a change to combination therapy inhaler Symbicort® (400 micrograms BDP-equivalent daily), depending on how the BTS/SIGN guideline is interpreted. A higher preference was given to an increase in the ICS dose (18/40 respondents; 45.0%) over the addition of a LABA to the current dose of ICS (14/40 respondents; 35.0%), although responses were split between delivery in one or two inhaler devices. Option for transitioning to a combination therapy inhaler at 1,000 micrograms BDP-equivalent daily was chosen

by 6 respondents (15.0%). The choice of LABA addition was most common among pharmacists (4/8 respondents; 50.0% of group), followed by GPs (5/16 respondents, 31.2% of group) and nurses (5/17 respondents; 29.4% of group).

For case 2, the patient presented with poorly controlled asthma as evident by a recent hospital encounter; the expected therapy options would again either be an increase in the budesonide dose (800 micrograms BDP-equivalent daily) or the addition of a LABA by changing to combination therapy inhaler Seretide® (400 micrograms BDP-equivalent daily). Respondents gave equal preference for increasing the ICS dose or switching to a combination therapy inhaler at 400 micrograms BDP-equivalent daily, both with 12 and 13 respondents each (30.8 and 33.3%, respectively). A higher dose of combination inhaler therapy at 800 micrograms BDP-equivalent daily and the choice to re-evaluate after the patient finished his course of prednisolone were less preferred. Among the top two choices, pharmacists preferred low-dose combination therapy to an increased dose of ICS (5 vs. 2 respondents; 62.5 vs. 25.0% of group), whereas nurses had relatively equal preference (6 vs. 5 respondents; 37.5 vs. 31.3% of group). In addition to an increased dose of ICS (5/15 respondents; 33.3% of group), GPs were the primary driver behind use of higher dose combination inhaler therapy (5/15 respondents; 33.3% of group).

Lastly with case 3, the presenting patient states intermittent use of her salbutamol inhaler and therefore, the expected answer would be no change to therapy. The majority of respondents did indeed choose no change to the regimen (21/43 respondents; 48.8%). Six respondents (15.0%) chose a step-down to 400 micrograms of BDP-equivalent daily and 8 respondents (20.0%) chose to step-up therapy with the addition of a LABA inhaler. Whereas the majority of GPs (11/14 respondents; 78.6% of group) and pharmacists (5/8 respondents; 62.5% of group) recommended no change in therapy, this was lower among nurses (5/16 respondents; 31.3% of group).

For the multiple-response ICS equivalency questions, the overall correct response rate was 61.4% (SEM: 5.0%) (Table 4.10). Answers referencing Clenil Modulite® and budesonide had a higher rate of correct answers compared to other products. A low proportion of GPs (6/16 respondents; 37.5% of group) identified Flixotide® as a

correct response for question 4.2, compared to nurses (14/17 respondents; 82.4% of group) and pharmacists (8/8 respondents; 100.0% of group). However, when Flixotide® was the subject of the question (question 4.3), GPs correctly identified equivalency with BDP-containing products at a higher rate (10/15 respondents; 66.7% of group). Overall, identification of the correct equivalencies was lower for the combination therapy question (question 4.4) compared to the single-agent ICS questions; this was particularly true for the proportion of GPs able to identify the equivalent dose between the two main licensed available combination therapy inhalers (26.7% of group). The only correct answer with an overall poor response (30.0%) was Qvar® for question 4.3, which was the only choice with a nonstandard dosing regimen (daily instead of twice a day); this was seen for GPs (4/15 respondents; 26.7% of group) and nurses (4/17 respondents; 23.5% of group) but less common among pharmacists (4/8 respondents; 50.0% of group). The overall correct response rate was 90.0% (SEM: 4.6%) for pharmacists, 67.7% (SEM: 5.9%) for nurses and 48.1% (SEM: 8.5%) for GPs ($p<0.05$ for pharmacists vs. GPs). Out of 14 total responses for "*Don't know*" across the four equivalency questions, GPs accounted for 11 responses (78.6%).

Table 4.10: Clinician survey responses (multiple response)
Expected responses highlighted

Question	Responses	n (%)
4.1 – Budesonide 200 mcg 1 puff BD	Qvar® 100 mcg 1 puff BD	27 (65.9)
	Clenil Modulite® 200 mcg 1 puff BD	33 (80.5)
	Flixotide Evohaler® 50 mcg 1 puff BD	4 (9.8)
	Beclometasone 100 mcg 1 puff BD	1 (2.4)
	Don't know	3 (7.3)
4.2 – Clenil Modulite® 100 mcg 1 puff BD	Budesonide 100 mcg 1 puff BD	35 (85.4)
	Asmanex® 100 mcg 1 puff BD	3 (7.3)
	Flixotide Accuhaler® 50 mcg 1 puff BD	28 (68.3)
	Qvar ® 200 mcg 1 puff BD	3 (7.3)
	Don't know	3 (7.3)
4.3 – Flixotide Accuhaler® 100 mcg 1 puff BD	Clenil Modulite® 200 mcg 1 puff BD	32 (80.0)
	Qvar ® 100 mcg 2 puffs daily	12 (30.0)
	Beclometasone 200 mcg 1 puff BD	30 (75.0)
	Budesonide 100 mcg 2 puffs BD	20 (50.0)
	Don't know	5 (12.5)
4.4 – Seretide Accuhaler® 100 mcg 1 puff BD	Symbicort® 200 mcg 1 puff BD	21 (52.5)
	Qvar ® 200 mcg 1 puff BD + Serevent Accuhaler® 1 puff BD	9 (22.5)
	Clenil Modulite® 200 mcg 1 puff BD + Serevent Evohaler® 2 puffs BD	26 (65.0)
	Budesonide 100 mcg 1 puff BD + formoterol 12 mcg BD	6 (15.0)
	Don't know	3 (7.5)

4.4.3 Discussion

The step classification analysis was able to provide several insights into the treatment of asthma. Although the step scheme is not meant to be a rigid directive for clinicians, using it to classify an asthma population provides a 'snapshot' of treatment in a real-world setting, as well as allowing for comparison across international cohorts. One previous analysis classified a UK cohort of approximately 17,000 adults to the 1993 BTS guideline by the type of therapy they were prescribed, and then re-allocated them based on identification of patients with poor control who could have their therapy stepped up (Neville *et al.*, 1999); notably, this analysis was conducted prior to the current recommendations for combination

therapy which were implemented in 2003. The analysis found that 74.6% of patients were treated either with SABA or low-dose ICS with only 6.3% and 4.5% of patients receiving more aggressive therapy in the form of high-dose ICS and low-dose combination therapy, respectively (Neville *et al.*, 1999). However, when patients with high utilisation of SABA were re-allocated the proportion of patients on aggressive therapy was predicted to nearly triple suggesting a large group of patients may have been sub-optimally treated (Neville *et al.*, 1999). A further smaller analysis of over 3,000 adults and children aged 5 and older in Nottinghamshire classified patients according to the 1995 BTS guideline and found similar results with 76% of patients receiving either SABA or low-dose ICS and 11% of patients receiving either high-dose ICS or low-dose combination therapy (Walsh *et al.*, 1999). The analysis also examined pharmacological measures of morbidity using SABA and OCS as markers and found these to correlate with increasing step, although patients with little or no preventive therapy still accounted for more than half of high doses of SABA/OCS (Walsh *et al.*, 1999). Outside the UK, a third analysis stratified 4,000 adults and children aged 6 years and older in France according to the 1995 GINA guideline based on a combined severity assessment of symptoms, FEV_1 and prescribed medication (Liard *et al.*, 2000). Using medication alone for classification, 46.8% of patients did not receive any preventer therapy, while an additional 19.7% of patients received low- or medium-dose ICS alone (Liard *et al.*, 2000).

Compared with these previous step analyses, treatment for adults in both the FV and KY databases has shifted toward higher step therapy particularly at step 4 with the use of high-dose combination therapy. While the previous analyses did not separate their patient populations into adults and children, nor were any conducted in in the USA, step 4 prescribing for children in the KY database was particularly high at 27.0% of the total cohort and nearly four-fold more than the FV database. The reasons for these changes in prescribing are unclear but many factors may contribute. Single-agent LABA inhalers have been available in the UK and USA since the early 1990s but the licensing of single-inhaler combination products and subsequent study data confirming the additive benefits of a corticosteroid and bronchodilator has helped push prescribing forward in step classification. Whether the identified prescribing is appropriate or not is the true question. Unfortunately, it is impossible to determine the clinical reasoning behind such therapy in this database analysis. The differential between the FV and KY database is likely a reflection of

the media concerns with ICS dosing and adrenal suppression in the UK as discussed previously. It is interesting to note that these data were disseminated outside of the UK through scientific literature, and therefore could (and arguably, should) have prompted the same safety scare in the USA. The main difference between the issue in either country was the enhanced coverage in UK popular (vs. scientific) media, which increased public awareness and empowerment from the patient aspect. Why this did not happen to the same degree in the USA is unclear. However, it is evident that the landscape of asthma prescribing has changed dramatically in the last ten years since the publication of previous literature and the present analysis provides evidenced momentum to develop further research evaluating prescribing behaviours.

Although approximately one-third of adult patients in both databases were classified at step 4, a similar proportion of patients in the KY database were also classified at step 1 with no preventer therapy. It is not clear whether these patients are being appropriately treated with no need for preventive therapy or if they are sub-optimally controlled. Compared with other steps, the patients on step 1 therapy received comparatively lower doses of SABA and courses of OCS. However, these are surrogate markers of symptoms and exacerbations and may not capture the full picture of asthma control if the patient fails to approach their GP for treatment or accepts a level of symptoms greater than defined in the guideline for step-up. Additionally, the KY database was formed from insurance claims data and included patients with medical claims attached to ICD-9 CM diagnosis codes for asthma. These codes may be attached to a claim inaccurately by mis-coding, or presumptively for a patient perhaps experiencing wheeze associated with an acute respiratory illness but not with a confirmed diagnosis of asthma. Some patients classified at step 1 perhaps should not be included in the classification. However, there is opportunity for the same scenario to have occurred within the FV database where patients have been entered onto the asthma register wrongly.

Of particular interest in the analyses was therapy utilised at step 3. The choice between increased doses of ICS versus early combination therapy remains somewhat debated thus it was thought that this area of the step classification might provide some understanding of how this debate and the guideline recommendations translate into real practice. The analysis found that for adults, medium-dose ICS

alone was preferred to low-dose combination therapy within the FV database, albeit by a small margin (38.1 vs. 32.6%), but for the KY database, low-dose combination therapy was largely preferred (51.7 vs. 16.1%). While the BTS/SIGN guideline in the UK has ambiguous recommendations for step 2/3 regarding the optimal dose of ICS at which to add a LABA, the NHLBI guideline in the USA has a clear equivalent recommendation for either an increase in ICS dose or the addition of a LABA, as well as a defined dosing range at which to consider said changes. The results are almost counterintuitive. For children, the BTS/SIGN and NHLBI guideline remain the same as for adults; despite this, medium-dose ICS was preferred in the FV database while ICS and LTRA was preferred in the KY database.

Children appear to have a different response to the therapy options for step 3. A recent Cochrane review included 48 trials comparing combination therapy (median dose of 400 micrograms BDP-equivalent daily) to a higher dose of ICS (median dose of 1,000 micrograms BDP-equivalent daily), including 14,000 adults and 1,155 children (Ducharme *et al.*, 2010). While for adults, combination therapy had a lower risk of exacerbations (RR: 0.88, 95% CI: 0.78-0.98), for children, combination therapy was associated with a trend toward greater need for rescue OCS (RR: 1.24, 95% CI: 0.58-2.66) and hospital admission (RR: 2.21, 95% CI: 0.74-6.64) although the number of patients limited statistical comparison (Ducharme *et al.*, 2010). However, the review acknowledged that evidence overall in children was "*less favourable towards LABA, and includes the possibility that increased steroids is superior in reducing the requirement for oral steroids and hospital admissions*" (Ducharme *et al.*, 2010). It should be noted that recommendations for children in this review was derived from no more than 24 events for OCS (out of 480 patients) and 12 events for hospital admissions (out of 1026 patients).

Interestingly, although the BTS/SIGN and NHLBI guidelines have similar recommendations for adults and children, the preferred therapies are different among the groups in this analysis. It is feasible that clinicians may reference other evidence and other guidelines in their clinical practice. For instance, the GINA asthma guideline makes a direct recommendation for combination therapy in adults and for medium-dose ICS or ICS with LTRA in children (Global Initiative for Asthma, 2012). Despite the fact that all three guidelines reference the same clinical studies,

their prescribing advice is varied and this analysis would support that this guideline variance has subsequently trickled down to create variability in clinical practice.

It should be noted that LTRA prescribing was not captured within the FV database. Campbell Software Solutions® exported medicines prescribed from participating GP practices based on the quality of the drug dictionary data in GPASS, only selected medications including inhaled therapies from BNF subsections 3.1 and 3.2 and oral corticosteroids in subsection 6.3 were mapped and included in the database (Lavery, 2012). A *post hoc* inquiry using the Prescribing Information System for Scotland (PRISMS; a subset of the PIS database) reported 10,395 prescriptions for LTRAs dispensed to both adults and children in the NHS Forth Valley Health Board during 2008 (NHS Scotland, 2012). The present analysis found over 2.5-fold the volume each of ICS and combination therapy inhalers were prescribed to patients for practices included in the FV database demonstrating the relative and likely preference for these therapies over LTRA. If any effect was anticipated, it would result primarily in a shift of paediatric patients from steps 1 and 2 to steps 2 and 3, respectively, within the FV database (patients that were identified as being on an ICS alone [step 2] but were additionally receiving an LTRA as add-on therapy not captured by the database [step 3]).

The differences in data sources (prescribing vs. dispensing) between the FV and KY databases has the ability to affect the results, although the qualitative classifications of treatment in this section (as opposed to quantitative) may be less affected by the difference in the data sources; however, the differences that are present will be more difficult to quantify. For instance, the step classification analysis stratifies the population based on the type of treatment they received. If the gap between prescribing and dispensing is constant across all medicines then the overall classification remains consistent. However, if ICS are more likely than SABA to be prescribed but not dispensed then step 2 will be particularly overestimated and the effect on the overall classification becomes inconsistent.

For patients starting new combination inhaler therapy, some unique insights into prescribing emerged within both the FV and KY databases. It was evident that a large proportion of patients were receiving high-dose combination therapy, as shown by proportion of patients treated at step 4 in the step classification analysis.

However, it was found that within the KY database, only one-fifth of patients had received an ICS in the year prior to a combination therapy inhaler. Similar findings have been noted in other analyses. A retrospective analysis of Canadian health claims found that among nearly 15,000 new users of combination therapy inhalers, only 39.6% had received an ICS product in the preceding year, and only 55.8% had received any previous asthma medication, including SABA, ICS, LABA, LTRA, theophyllines or OCS (Breton *et al.*, 2007). Similarly, two further retrospective studies in the USA looked at patients with new combination inhaler therapy and identified the proportion of patients with qualifying reasons to start said therapy, as shown by previous treatment with an ICS or LTRA, an asthma-related emergency visit or hospitalisation, or use of at least two courses of OCS or 6 canisters of SABA in the previous year (Blanchette *et al.*, 2009; Ye *et al.*, 2009). Only 39.2% of patients fulfilled at least one criterion, which was higher for patients treated with budesonide/formoterol (55.6%) compared to those treated with fluticasone/salmeterol (37.7%) (Blanchette *et al.*, 2009). A lack of appropriate step-wise management prior to initiating combination therapy has been previously identified as a widespread problem, as the present analysis found within the KY database.

Alternatively, over three-quarters of patients in the FV database were found to have received treatment with an ICS prior to combination therapy inhaled initiation, which we believe is the first assessment of such prescribing within a real-world UK cohort This suggests a better concordance with guideline recommendations in NHS Forth Valley compared to Kentucky. However, unlike previous analyses describing appropriateness of combination therapy initiation, the present analysis also looked at the dose changes occurring at the transition from ICS to combination therapy; it was found that within the FV database, there was a widespread pattern of ICS dose escalation on addition of a LABA to the therapy regimen, with patients advancing directly to high-dose combination therapy largely irrespective of their baseline ICS dose. Although the number of patients analysed was much lower, the same trend was not present within the KY database, where patients generally had either similar or a decreased dose of ICS on transition to combination therapy.

There is some thought that the ‘culture’ surrounding asthma treatment between the UK and USA is different, even beyond textual differences in the clinical guidelines.

Nearly 30 years ago, these differences were identified, and the progressive and pioneering approach to asthma treatment within the UK lauded compared to the USA (Clark, 1986). Unfortunately, more modern and direct comparisons between the two countries are few and far between. One randomised controlled trial identified potential differences in outcomes based on which treatment algorithms were used for the treatment of acute severe asthma finding the higher doses of SABA in the USA led to greater initial improvement in lung function while the lower doses of OCS in the UK were equally efficacious in the long-term for recovery (Innes *et al.*, 2002). Other useful comparisons are needed to answer the question fully, such as the attitudes/opinions of clinicians, direct comparisons of guideline adherence and the relative influence of regulation (from the MHRA and FDA) on treatment patterns. However, data from patients initiating combination therapy in the present analysis may provide support that a more aggressive real-world treatment approach exists in the UK compared to the USA – whether or not this is supported by clinical guidelines.

Patients with no history of ICS in the year prior to combination therapy in the KY database (the majority of the cohort) broke with trend and were unusually changed to high-dose combination therapy at a rate similar to that in the FV database (51.1% and 56.3% of the ICS category, respectively). Widespread high-dose ICS prescribing is of particular concern due to the fact that the adverse effects of ICS such as hypothalamic-pituitary-adrenal (HPA)-axis suppression, decreases in bone mineral density and skin bruising are more common at this dose range (Kelly *et al.*, 2003; Lipworth, 1999). As a database analysis, it is impossible to determine the clinical reasoning underlying ICS dose changes, and the suitability of said therapy changes. Although the BTS/SIGN guideline provides a step-wise approach to asthma treatment, it does recommend that patients should start treatment on the step most appropriate to their asthma therapy (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2012). Patients who are prescribed high-dose therapy may require it to establish and maintain good control of their disease. However, there is an abundance of high-quality evidence that suggests that the majority of therapeutic benefits of ICS are seen at a moderate dose of 500 micrograms of BDP-equivalent daily, with the maximum effect attained at 1,000 micrograms BDP-equivalent daily (Holt *et al.*, 2001; Masoli, Holt*, et al.*, 2004). Furthermore, the BTS/SIGN guideline does not provide an objective means to

determine the most appropriate step for therapy. It is therefore possible that a large proportion of patients on high-dose therapy are being treated inappropriately rather than legitimately requiring such therapy for control.

Database studies fail to capture the full picture of prescribing from both the patient and clinician perspective. Results from the clinician survey indicate that understanding of the BTS/SIGN guideline may play an important role in the treatment of asthma. Asthma is generally thought to be a heterogeneous disease that requires a clinician to design an individualised treatment plan for a patient to achieve optimal control. While the BTS/SIGN asthma step scheme provides evidence-based guidance, variation in treatment practice is expected. However, identifying potential areas for improvement in clinician education remains an important goal for quality improvement.

A number of analyses have investigated physician knowledge and application related to asthma guidelines and found variable but generally poor rates of concordance with optimal practice (Boulet *et al.*, 2002; Cicutto *et al.*, 2000; Doerschug *et al.*, 1999; Finkelstein *et al.*, 2000; Gourgoulianis *et al.*, 1998). The bulk of these analyses were performed around 15 years ago, and there is a paucity of more recent data. An analysis in Spain assessed attitudes toward and application of national asthma guidelines and found that only 33% of physicians and nurses could demonstrate knowledge on how to adjust maintenance therapy dosages (Plaza *et al.*, 2008). Among Canadian physicians, there was good evidence of appropriate step-up in therapy, but only when they were able to correctly identify patients with poorly controlled disease, which failed to occur in nearly 30% of cases (Chapman *et al.*, 2008). Analyses specifically from within the UK are rarer, but have demonstrated a lack of treatment ‘step up’ after an exacerbation, inadequate emergency treatment and secondary care referral and a lack of guideline implementation despite demonstrated awareness of recommendations (Neville *et al.*, 1993; Pinnock *et al.*, 1999; Wiener-Ogilvie *et al.*, 2007).

With these data in mind, case-based questions were designed to achieve two goals: discern the ability of respondents to classify a patient according to the BTS/SIGN step scheme and identify preferences for different treatment options. Notably, these questions centred on treatment at step 2 and 3, where previous ambiguity had been

perceived within the guideline. The large majority of respondents were able to meet the first goal. However, for the second goal, some useful information emerged.

The first two cases described patients with uncontrolled asthma on step 2 therapy, the second of which was recently post-exacerbation. With historical evidence to support the use of increased doses of ICS to specifically reduce the risk of future exacerbations (Pauwels *et al.*, 1997), it was hypothesised that this might be the preferred response in the second case, while the guideline-recommended addition of a LABA would be preferred in the first case. In actuality, the opposite was almost true – an increased dose of ICS was the preferred therapy for the first case, while an equal preference for an increased dose of ICS or a combination therapy inhaler was preferred in the second case. Even with these choices highly favoured, other options accounted for 34.2% and 30.6% of responses for questions 1.2 and 2.2, respectively, indicating a high variety of treatment preferences overall. The reasons for this are unclear from the survey. The third case described a patient with relatively infrequent symptoms, who could be eligible to consider therapy step-down. While just over half of respondents preferred to keep the patient on current therapy, only 15.0% considered a reduction in therapy their preferred choice. Despite reduction in therapy remaining a guideline recommended consideration for patients with stable asthma, there appears to be hesitancy to employ such action likely for fear of disrupting the patient's disease control. Indeed, reduction in asthma therapy has been the subject of several recent studies. For patients on high-dose ICS, a 50% reduction in dose is possible without increasing exacerbations or healthcare visits, or reducing health status (Hawkins *et al.*, 2003). Additionally, stepping down from a high-dose combination therapy inhaler to a low- or medium-dose combination therapy inhaler was found to be similarly feasible (Papi *et al.*, 2012). This is likely reflective of the dose-response curve seen with ICS where reduction of higher doses results in negligible differences in disease control. Although the patient in question for case 3 was on a moderate-dose of ICS, the lack of consideration of step-down amongst respondents (even less than the proportion of respondents who opted to step-up therapy in a well-controlled patient) may suggest an additional area to target for clinician education.

Despite some successes with stepping down therapy, rapid tapering or complete discontinuation of ICS generally does result in disease deterioration (Haahtela *et al.*,

1994; Waalkens *et al.*, 1993). A recent landmark meta-analysis found that among patients controlled on a range of doses of combination therapy, removal of the LABA component resulted in reductions in quality of life, worse disease control and more symptoms compared to patients with no change in treatment (Brozek *et al.*, 2012). This latter finding has been particularly important as current prescribing advice from the MHRA (in the UK) and black-box warnings on LABAs from the FDA (in the USA) continue to recommend discontinuation of the agent once asthma control has been achieved – despite evidence that this might be a less than optimal approach. While specifically studied for combination therapy, hesitancy to step-down treatment may be infiltrating all aspects of asthma therapy.

There was suggestion that nurses and pharmacists had a better understanding of ICS products compared to GPs as reflected by better performance on ICS equivalency questions. Data for general practice consultations in Scotland at-large indicate that the ratio of general practice consultations for asthma performed by practice nurses to GPs was 1.42 in 2012/13, and has been above 1.00 since 2005/06 (Practice Team Initiative, 2013c). Similarly, nurses in the clinician survey indicated a higher frequency of treating patients with asthma than did GPs. With greater exposure to asthma patients in daily practice, practice nurses likely have increased familiarity with the guideline and ICS products used in treatment. Familiarity may also explain why questions/responses referring to Clenil Modulite® had a higher pattern of correct responses compared to other products, as it is the most utilised ICS in the health board and across Scotland. Nonetheless, GPs still accounted for over 40% of asthma consultations and ICS other than Clenil Modulite® represented more around 60% of prescribing volume in NHS Forth Valley, indicating that these may represent areas for optimisation.

Based on the high prevalence of high-dose combination therapy noted in previous analyses looking at step classification and initiation of combination inhaler therapy, it was hypothesised that a lack of awareness of the potency of fluticasone-containing products might be a contributing factor. Fluticasone has been implicated as a potential motivator behind high-dose prescribing previously, specifically in children (Thomas *et al.*, 2006). Although it appears to be solely a function of the product's potency other ICS products with similar potency such as Qvar® and mometasone have not been implicated in previous studies nor do they seem to have contributed

greatly to high-dose prescribing in the current analyses. Both products have licensed dosing up to 1,600 micrograms daily BDP-equivalent (compared to fluticasone up to 2,000 micrograms daily BDP-equivalent) leaving the opportunity for such use. Within the NHS Forth Valley formulary, beclometasone and budesonide are recommended as 1st and 2nd line ICS products, respectively, with fluticasone available as an alternate (Forth Valley Area Drug and Therapeutics Committee, 2012). The non-formulary status of mometasone makes it likely that this product is used rarely and therefore has little potential to contribute to high-dose prescribing. However, why Qvar® fails to have the same influence as fluticasone is unclear.

The case-based questions required clinicians to simultaneously identify the presence or lack of asthma control, apply evidence-based recommendations to choose therapy and to be aware of available licensed products and their potencies. While the ICS equivalency questions should have separated out knowledge gaps present from the latter, it is not possible to say from the survey whether deviations in practice from guideline recommendations are the result of a lack of knowledge and understanding, or simply personal preferences among individual clinicians. Additionally, questions were intentionally written to be brief and succinct, and therefore did not contain details regarding the patient's history that may have been desired in real clinical practice to make therapy decisions. However, a free-texted '*Other (please specify)*' field was made available to attempt to capture clinicians who had further inquiries or considerations regarding the questions; this option was selected in less than 10% of responses to case-based questions.

4.5 Conclusion

Patients with asthma were found to have significant barriers with regard to optimal treatment. Adherence and persistence with chronic medication was found to be low and suggestive of intermittent use of therapy. The use of high-dose combination therapy was particularly rampant in the FV database, often without sufficient treatment history that would support its use. Although the use of this dose of therapy was less common in the KY database, most patients had no record of previous therapy. Lastly, data from the clinician survey on asthma showed that opinions regarding application of the guidelines and knowledge of ICS dose equivalences were variable.

Chapter 5:

COPD

5.1 Introduction, aims and objectives

A second, similar set of analyses was undertaken for patients with COPD in the FV and KY databases. Changes were made to reflect the different nature of the disease state, particularly with regard to analyses regarding treatment investigation. An additional analysis was also undertaken to assess utilisation of spirometry. Lastly, patients with COPD were compared to patients with asthma in the FV database to assess differences in adherence/persistence. The objectives of this chapter were:

- Compare the demographics of the two populations of patients with COPD;
- Describe medicine utilisation in terms of general utilisation and with categorisation into options recommended in the NICE guideline;
- Quantify levels of adherence and persistence with respiratory medicines and evaluate the effect of diagnosis on these behaviours;
- Evaluate the use of spirometry within NHS Forth Valley;
- Identify areas for quality improvement in the clinical care of COPD in NHS Forth Valley and Kentucky.

5.2 Demographics

5.2.1 Methods

Demographic data for age, sex, prevalence, smoking status and socioeconomic deprivation from January 2007 – December 2009 for patients with COPD was analysed using the same methods as those with asthma (as described in detail in section 4.2.1), with a single alteration. Age distributions were again constructed with 10-year age bands, however the terminal categories were changed to less than 40 years old and greater than or equal to 90 years old; this was performed to better reflect the usual time course of COPD within a patient's lifespan. This change is reflected throughout all COPD analyses.

Spirometry data were also analysed for patients with COPD in the FV database. Two queries were conducted. First, quantifying the number of patients with both FEV_1 and FVC data and therefore the ability to calculate an FEV_1/FVC ratio, and secondly, quantifying the number of patients with FEV_1 % predicted data during the three-year period (queries 31 – 32). FEV_1 % predicted data were analysed both as a

continuous variable (using median and interquartile ranges) and by classification into airflow limitation severity categories, as described in the NICE COPD guideline (National Institute for Health and Clinical Excellence, 2010). As a patient may have had multiple test results for spirometry during the study timeframe, the highest values for each patient were utilised for stratification. Data were compared by sex and age classification, and statistical significance assessed using 2-proportion (with Bonferroni correction) and Mann-Whitney tests.

5.2.2 Results

5.2.2.1 Age, sex and prevalence

Five thousand three hundred and eighty-six distinct patients with COPD were treated between 2007 – 2009 in the FV database; 2008 was the best populated with 4,650 patients. A total of 920 (17.1%) patients were concurrently listed on the asthma register. Women represented the slight majority of patients (51.5 vs. 48.5%), and were marginally younger with a median age of 68 years (IQR: 59 to 75 years) compared to men at 69 years (IQR: 61 to 76 years; p=0.0011). The age distribution of patients with COPD was largely similar between the sexes, with the highest percentage of women at 60 to 69 years of age (31.1%) and the highest percentage of men at 70 to 79 years of age (34.1%) (Figure 5.1). Women had a larger proportion of patients identified in the 50 to 59 year old category while men had a higher proportion of patients in the 70 to 79 year old category.

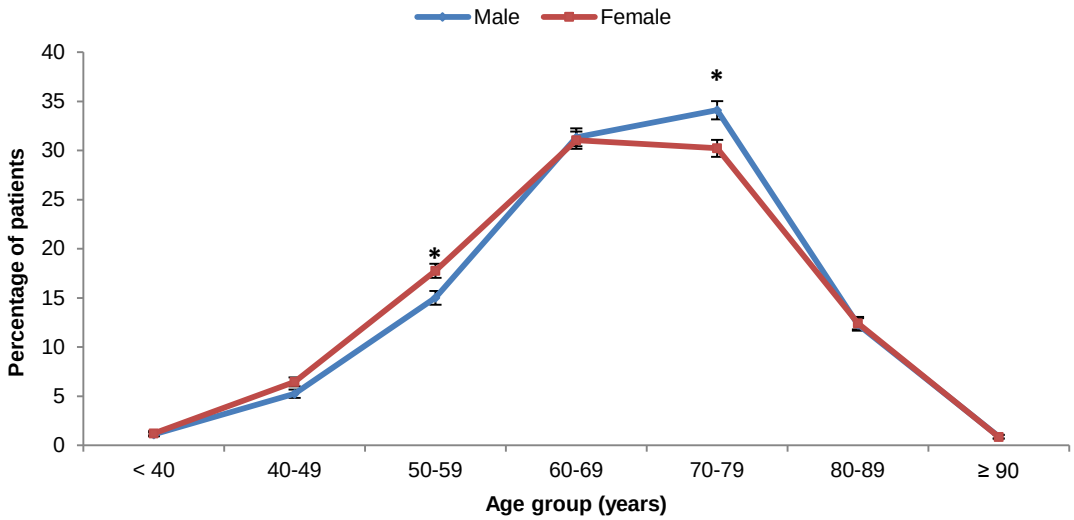


Figure 5.1: Age distribution of patients with COPD in the FV database by sex (2007 – 2009)
** p<0.05 for the difference between men and women*

A total of 3,715 distinct patients with chronic bronchitis, emphysema or COPD were identified in the KY database between 2007 and 2009, including the 1,110 (29.9%) patients with concurrent claims for asthma. Women again made up the slight majority of patients (51.4%) with an overall younger age of 52.5 years (IQR: 44 to 60 years) compared to men at 54 years (IQR: 45 to 62 years; p<0.001). The age distribution was similar among men and women with the exception of the 60 to 69 year old age group, where men were a larger proportion of patients than women (20.7 vs. 17.2%, p=0.049).

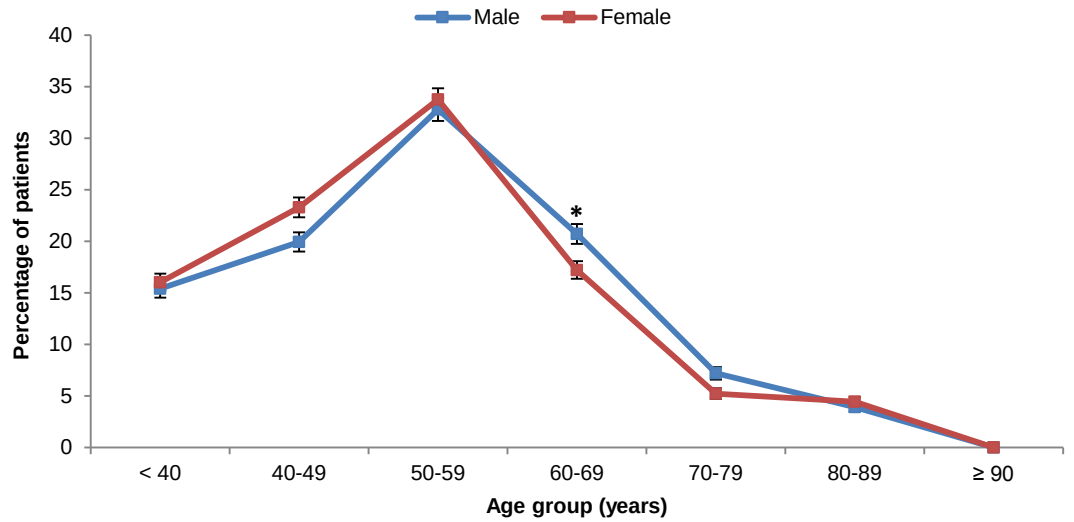


Figure 5.2: Age distribution of patients with COPD in the KY database by sex (2007 – 2009)
** p<0.05 for the difference between men and women*

A demographic comparison of age and sex distributions between the FV and KY databases showed some significant differences (Figure 5.3). The peak proportion of patients of either sex in the KY database was identified 1 to 2 decades before that of the FV database. Additionally, nearly 16% of all patients (7.5% from men and 8.2% from women) in the KY database identified with COPD were less than 40 years of age in stark comparison to the FV database where this was the case for approximately 1% of all patients (0.5% for men and 0.6% for women). Of these unusually young patients in the KY database approximately half of them (312 patients; 53.4%) were aged 30 to 39 years old and a further 19.2% were aged 20 to 29 years old.

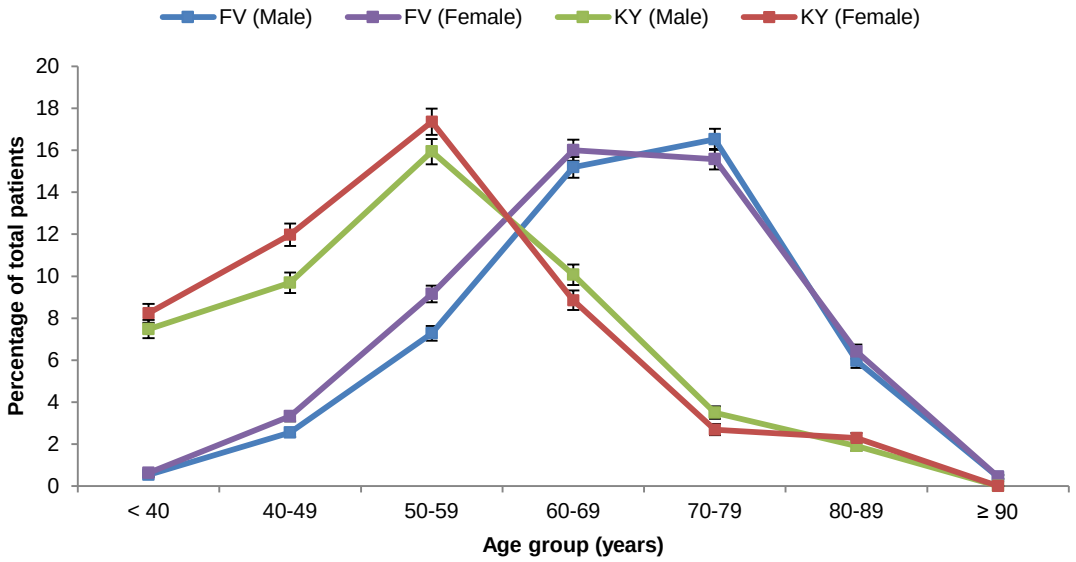


Figure 5.3: Comparison of age/sex distributions of patients with COPD in the FV and KY databases (2007 – 2009)

The standardised prevalence estimates for the FV database were similar between sexes at 2.0% across all ages for both men and women (p=0.423) and 4.0% and 3.8% for men and women aged 40 and older, respectively (p=0.144). Men had a higher prevalence than women at 70 years of age and older peaking at 11.8% at 80 to 89 years old (Figure 5.4). Women were shown to have a lower overall prevalence although with some suggestion of these estimates matching or outpacing men at younger ages; such was the case at 50 to 59 years old with the prevalence in women at 2.5% compared to men at 1.9% (p=0.014).

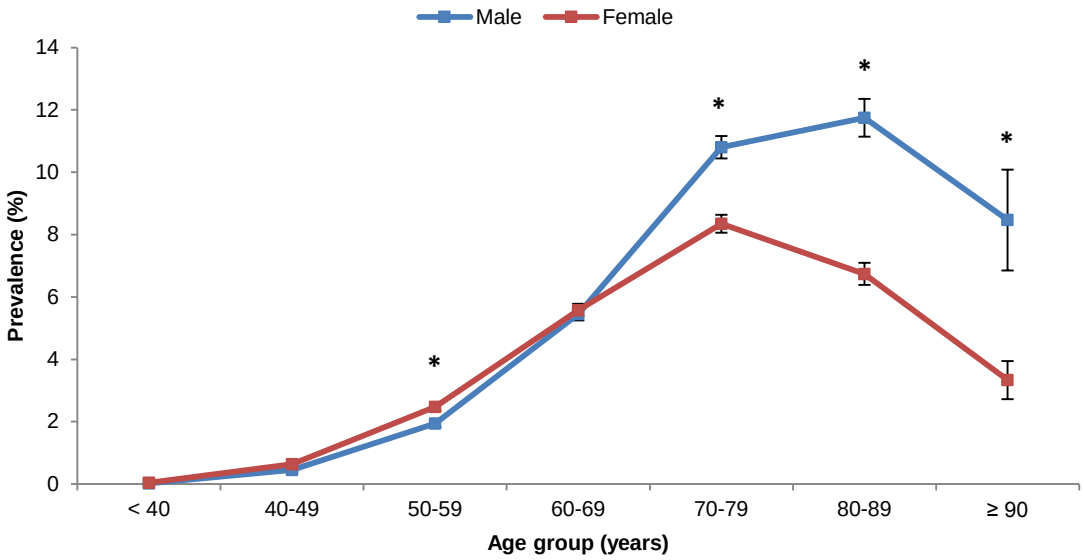


Figure 5.4: Prevalence of COPD in the FV database by age and sex (2008)
** p<0.05 for the difference between men and women*

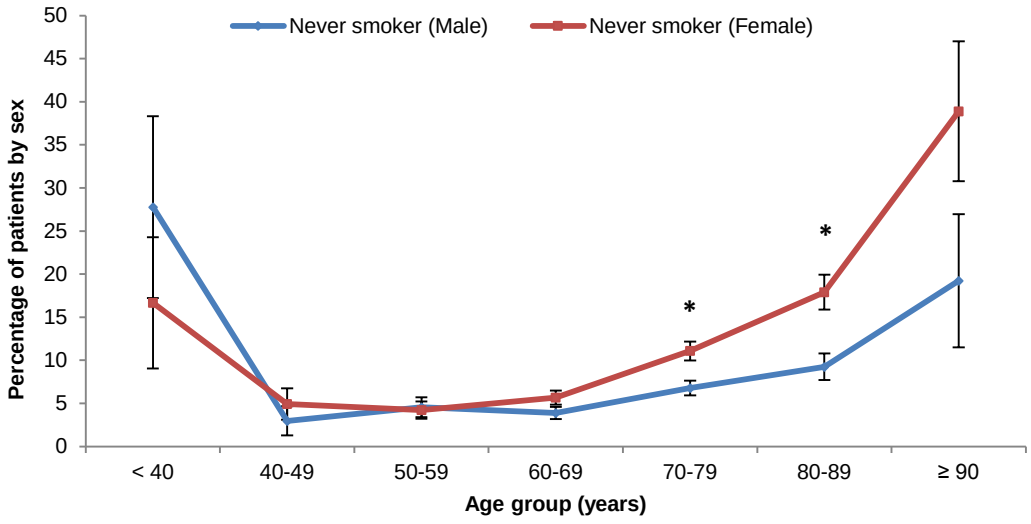
5.2.2.2 Smoking status

Data for smoking status were available for 5,045 patients (93.7%) in the FV database from 2007 – 2009 with the percentage capture increasing significantly from 2007 to 2008 and stabilising thereafter (Table 5.1). Across all three years just under half of patients were classified as former smokers (45.2%) followed by a considerable number of current smokers (36.6%). A small number of patients (7.8%) were classified as never smokers and the remaining patients (10.4%) had multiple smoking statuses recorded over the three year time period.

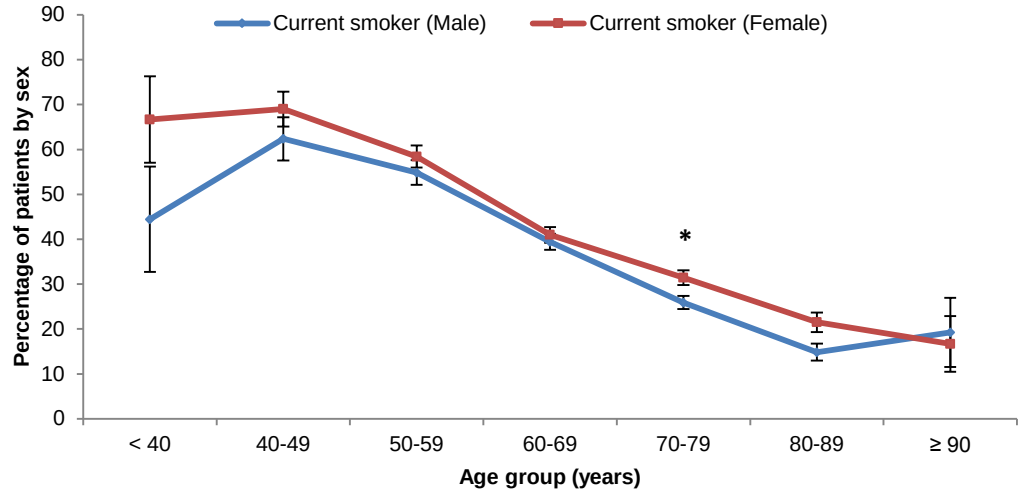
Table 5.1: Smoking status of patients with COPD in FV database (2007 – 2009)

Smoking status	**n (%)**		
	2007	**2008**	**2009**
Never smoker	172 (8.9)	240 (7.1)	246 (7.1)
Current smoker	748 (38.9)	1,354 (40.2)	1,406 (40.5)
Former smoker	973 (50.6)	1,677 (49.8)	1,728 (49.8)
Total	**1,922 (45.4)**	**3,370 (72.5)**	**3,468 (75.2)**

Smoking status varied by age and sex. More women were classified as current smokers (39.4 vs. 33.8%, $p<0.001$) while more men were classified as former smokers (60.1 vs. 51.2%, $p<0.001$). The small percentage of patients who had never smoked favoured women at 9.4% compared to 6.1% ($p<0.001$). When stratified according to age, never smokers were most commonly found at terminal ends of the age spectrum with 21.4% of all patients aged less than 40 years old and 30.7% of all patients aged 90 years old or greater. The prevalence of never smokers was particularly evident for women in later years (Figure 5.5(a)). For current smokers differences between the sexes were largely negligible with the percentage of total current smokers in each age group decreasing with increasing age from a peak of 66.3% among 40 to 49 year olds to 17.7% among those aged 90 years old or greater (Figure 5.5(b)). Former smokers showed the opposite trend with an increasing prevalence according to age ranging from 21.4% for patients less than 40 years of age to 68.2% for patients aged 80 to 89 years (Figure 5.5(c)). Rates were higher for men aged 70 to 89 years of age compared to women.



(a)



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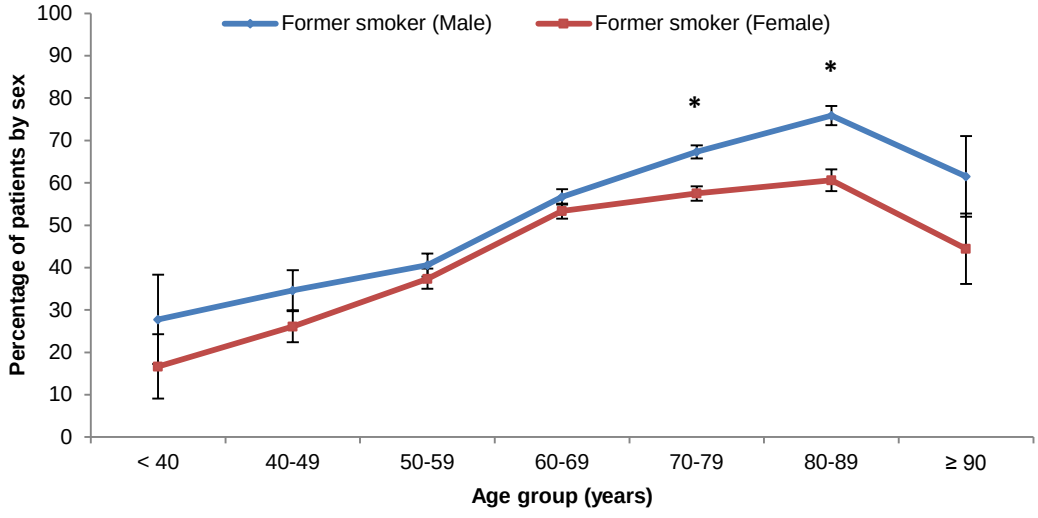


(c)

Figure 5.5: Age and sex distribution of patients with COPD in the FV database (2007 – 2009) for **(a)** never smokers, **(b)** current smokers and **(c)** former smokers

** p<0.05 for the difference between men and women*

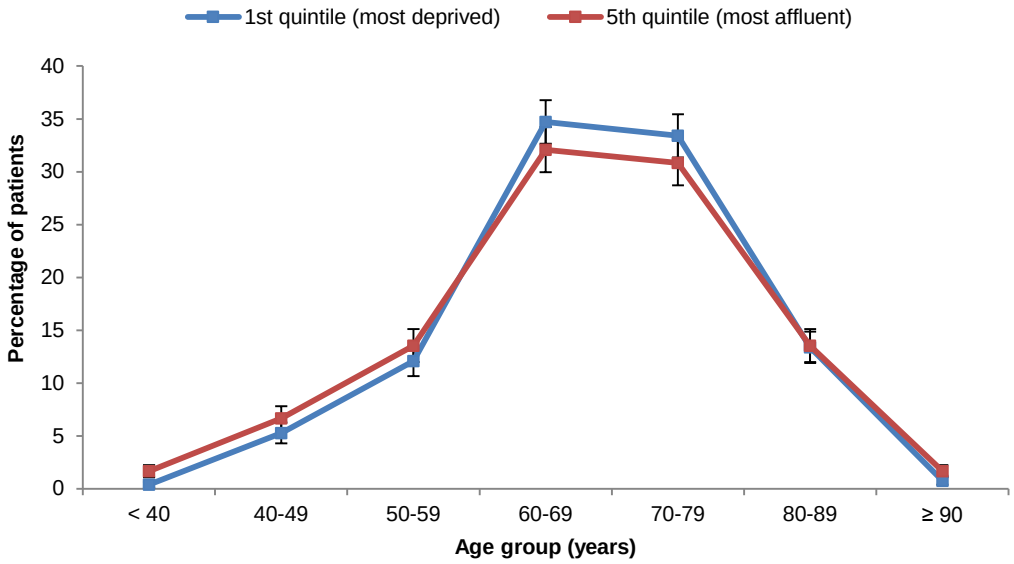
5.2.2.3 Deprivation

SIMD scores matched to GP postcode were available for all 5,386 patients with COPD in the FV database. Patients were socioeconomically diverse with slightly more than expected proportions in the more affluent end of the spectrum (Table 5.2). No statistical differences were seen between men and women.

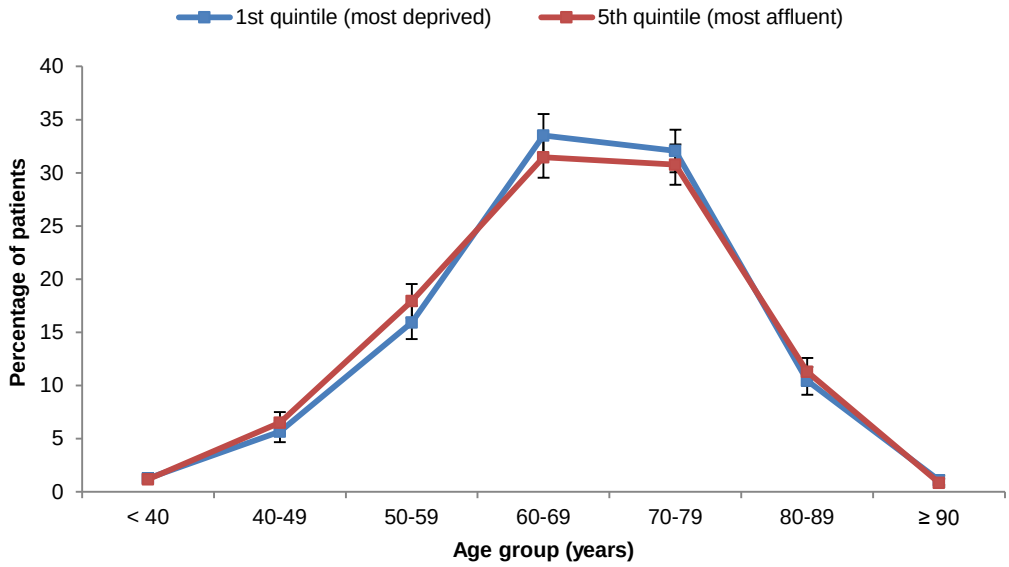
Table 5.2: SIMD quintile of patients with COPD in FV database by sex (2007 – 2009)

SIMD score	n (%)	
	Male	Female
1st quintile (most deprived)	530 (20.3)	546 (19.7)
2nd quintile	238 (9.1)	230 (8.3)
3rd quintile	846 (32.4)	920 (33.1)
4th quintile	516 (19.8)	495 (17.8)
5th quintile (most affluent)	480 (18.4)	585 (21.1)

When deprivation was assessed jointly with age and sex no differences were apparent between terminal SIMD quintiles (Figure 4.6(a) and (b)). There was some indication that patients from the most deprived SIMD quintile had a higher prevalence at the peak ages for COPD (60 to 79 years in this cohort) while patients from the most affluent SIMD quintile had higher prevalence within older and younger age categories; however, these differences were small and not statistically significant.



(a)



(b)

Figure 5.6: Age and deprivation distribution of patients with COPD in the FV database (2007 – 2009) for **(a)** men and **(b)** women

5.2.2.4 Spirometry

Joint data on FEV_1 % predicted and FVC was available for 2,746 tests associated with 2,250 patients (41.8%) for the three-year period. The median FEV_1/FVC ratio across all patients was 0.61 (IQR: 0.50 to 0.70) and a total of 75.2% of patients had FEV_1/FVC ratios of less than 0.7 which would be diagnostic of COPD.

A total of 6,513 FEV_1 % predicted data entries were available for 4,003 distinct patients (74.3%) in the FV database across all three years assessed with an overall median FEV_1 % predicted of 64% (IQR: 51 to 76%). The percentage of patients with an FEV_1 % predicted value recorded in a given year (regardless of other spirometry values) increased steadily from 2007 – 2009 (Table 5.3). Just over half of patients (58.0%) across all three years were classified according to the NICE classification as moderate COPD, followed by mild COPD and severe COPD each accounting for nearly one-fifth of patients (19.6% and 19.1%, respectively); the relative spread of COPD severity was stable across all three years.

Table 5.3: Classification of airflow limitation severity of patients with COPD in FV database (2007 – 2009)

Stage	**n (%)**		
	2007	**2008**	**2009**
1 (mild)	261 (15.5)	396 (16.4)	428 (15.8)
2 (moderate)	966 (57.4)	1,353 (56.1)	1,554 (57.3)
3 (severe)	376 (22.3)	559 (23.2)	608 (22.4)
4 (very severe)	80 (4.8)	104 (4.3)	123 (4.5)
Total	**1,683 (39.8)**	**2,412 (51.9)**	**2,713 (58.8)**

Women had an overall higher median FEV_1 % predicted than men at 66% (IQR: 54 to 77%) compared to 62% (IQR: 49 to 75%; $p<0.001$). When classified according to COPD severity categories, women had a higher proportion of patients classified as mild COPD (21.6 vs. 17.2%, $p<0.001$) and men had more patients classified as severe (21.4 vs. 16.8%, $p<0.001$) or very severe COPD (4.6 vs. 2.2%, $p<0.001$). The percentage of patients with moderate COPD was similar between men and women at 56.8% and 59.4%, respectively ($p=0.102$).

FEV_1 % predicted was variable according to age. In general, median FEV_1 % predicted decreased steadily with age from 72% (IQR: 59 to 80%) for patients aged 40 to 49 years old to 58% (IQR: 41 to 74%) for patients aged 90 years and greater. Patients less than 40 years of age were distinct from this trend with a lower than anticipated median FEV_1 % predicted of 60% (IQR: 54 to 78%). Classification of COPD severity additionally varied with age (Figure 5.7). Terminal age categories were subject to larger than expected proportions in some severity categories such as the large percentage of patients less than 40 years of age with very severe

COPD (7.4%) or the large percentage of patients greater than or equal to 90 years old with severe COPD (43.8%); this was likely due to the small number of patients assessed in either age group at 27 and 16 patients, respectively. Beyond these age groups, mild/moderate COPD was generally more common among younger ages and severe/very severe COPD more common in older age.

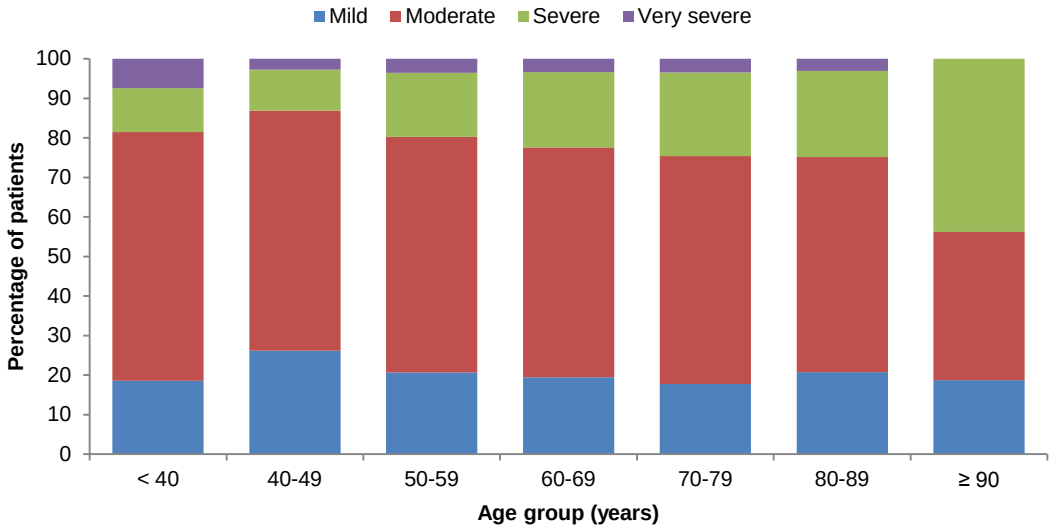


Figure 5.7: Airflow limitation severity and age distribution of patients with COPD in the FV database (2007 – 2009)

5.2.3 Discussion

The development of COPD is closely linked to a history of tobacco smoking although the pathological changes in resulting in airflow limitation are often not realised until after long-term and consistent exposure and after lung function has already decreased significantly. The peak age groups for COPD in the FV and KY databases were separated by 10 to 20 years suggesting that exposure for patients in the KY database was perhaps encountered earlier in life or perhaps to a more significant degree resulting in earlier onset of disease.

Differences in COPD prevalence may result from geographical distribution of genetic causes, such as alpha-1-antitrypsin deficiency. The distribution of genetic variants causing this disease is relatively stable among people of European ancestry and is therefore similar in UK and USA populations (Luisetti *et al.*, 2004). Because of this and its position as a relatively rare cause of COPD, genetics are unlikely to contribute largely to geographical differences in COPD prevalence. Differences in behaviours regarding tobacco use would be the most important and obvious factor

to consider. Smoking prevalence in Kentucky is highest among all states in the USA at 29% (Centers for Disease Control and Prevention, 2012). Furthermore, Kentucky ranks highly in current tobacco use among youths (in grades 9 to 12, corresponding to 13 to 17 years old) estimated at 31.9% and adults reporting exposure to second-hand smoke within the last 7 days at 51.4% (Centers for Disease Control and Prevention, 2012). Although not directly comparable due to differences in how the surveys were administered and how the data were collected, smoking prevalence in NHS Forth Valley and Scotland at-large is estimated at 25% (The Scottish Government, 2012a). Among 15-year olds in NHS Forth Valley, approximately 12% are regular smokers and a further 7% are occasional smokers (compared to 13% and 6% in Scotland at-large, respectively) (Information Services Division Scotland, 2011). Seventeen percent of adult non-smokers in Scotland reported second-hand smoke exposure in home environments and 16% reported exposure in public places although the latter figure has significantly decreased in recent years due to the ban on smoking in public places introduced across Scotland in 2006 (The Scottish Government, 2012b). The state of Kentucky lacks comprehensive legislation regarding public tobacco use although 38 municipalities (similar to councils in Scotland) across the state have enacted public smoke-free legislation on the local level (Blackford, 2014).

Kentucky continues to sustain its image as a ‘tobacco state’. In the last national census, the state contained the largest number of tobacco farms across the country at 8,113 (50% of total in the USA) and the second largest total tobacco land area at 87,641 acres (24.3% of total) (US Department of Agriculture, 2009). Because of a rich economic investment in tobacco the state excise taxation on cigarettes remains near the lowest in the USA at $0.60 (approximately £0.37) per pack of cigarettes; this is reflected across other tobacco-producing states which have an average tax of $0.49 (£0.30) per pack compared to non-tobacco-producing states at an average of $1.67 (£1.02) per pack (Campaign for Tobacco-Free Kids, 2013). On average, with the addition of a federal cigarette tax of $1.01 (£0.62) a pack of cigarettes in the USA costs a consumer roughly $6.03 (£3.68) (Campaign for Tobacco-Free Kids, 2013). This compares to an average recommended retail price in the UK of £7.98 per pack of which taxation constitutes 77% (Tobacco Manufacturers' Association, 2013). Good quality evidence shows that taxation effectively reduces both the prevalence and quantity of tobacco use with an estimated 3 to 5% decrease in

overall cigarettes consumed for every 10% increase in price (US Surgeon General, 2014); the two-fold difference in pricing between the UK and USA is important with regard to tobacco use behaviours. The higher rates of youth and adult tobacco use, second-hand exposure particularly in public spaces and decreased cost of tobacco in Kentucky compared to Scotland may have significant influence.

It is difficult to say that differences in tobacco culture completely underwrite the variation in peak age for patients with COPD in the FV and KY databases particularly as the current demographics would be the result of historical tobacco use due to the time lag between exposure and disease development. Additionally, the way tobacco is utilised may be important. For instance, the prevalence of roll-your-own tobacco smokers in the UK has been estimated at nearly four times the prevalence in the USA (28.4 vs. 6.7%), largely thought to be due to the lower price of commercially-made cigarettes in the USA (Young *et al.*, 2006). As roll-your-own tobacco is commonly smoked without a filter, it could feasibly be considered more dangerous with respect to toxin exposure and subsequent respiratory health risk. How this balances with prevalence to determine the development risk of COPD in either population is unknown.

As discussed previously, Scotland and the Forth Valley area had a rich industrial history in the middle of the 20th century, which tapered off thereafter with economic decline in mining, ship building and other heavy industries. Interestingly, Kentucky has a similar contribution of exposure particularly with regard to longstanding and continuing involvement of coal mining within the state. However, unlike Scotland, coal continues to feature as a major industry in Kentucky with peak production of 179.4 million tonnes from 85 mines as recently as 1990 (at over twice the amount mined in 1950); at this time, over 30,000 miners were employed in the state (Kentucky Office of Energy Policy *et al.*). Furthermore, approximately 60% of coal mining output in Kentucky remains in the form of underground (deep) mining which is thought to heighten exposure to respirable coal dust and increase the risk of lung disease (Kentucky Office of Energy Policy *et al.*). The continued influence of the coal industry in Kentucky compared to the historical nature of the industry in Scotland may also help explain the younger age of patients with COPD in the area.

The COPD demographics analysis shows that, like the asthma analysis, the patients included are a relatively typical patient population with COPD. The deprivation analysis showed a slight skew of patients towards more affluent socioeconomic areas but the NHS Forth Valley Health Board contains a mixed geographical area with both a rural spread as well as a couple of larger size towns positioned between the two main population centres of Scotland in Glasgow and Edinburgh; this is largely representative of many areas of the UK and the rest of the world although it may fail to capture some of the heavily deprived patients that are more commonly found in densely-populated urban areas.

Of interest may be the discovery that only three quarters of patients with FEV_1/FVC data had ratios less than 0.7, which is considered diagnostic for COPD, despite all patients being listed on practice COPD disease registers. Spirometry results recorded in the FV database include a mixture of both initial values as well as follow-up assessments and therefore reflect some fluctuation over time. The progressive nature of respiratory decline in COPD would indicate that the FEV_1/FVC should always remain less than 0.7 once diagnosed regardless of treatment. RCTs benefit in their study design from stringent inclusion/exclusion criteria which increase the internal validity, or the ability to ascertain that a particular outcome is directly the result of a specific exposure. The same methods can attempt to be applied to retrospective designs, which in this case, may have incurred the exclusion of patients without a diagnostic FEV_1/FVC ratio to verify COPD. However, the decision was made to include these patients as part of the 'COPD population' because regardless of their diagnostic validity, these are patients are included on the practice disease register and are treated as if they have COPD in real practice, and would be the type of patient excluded from almost all other types of study. It was felt that keeping these patients would shed light on a patient population otherwise ignored. However, it must be recognised that this may also dilute the study with patients who do not truly have the disease, lessening internal validity.

Because of the level of detail in the spirometry data it is not possible to tell whether the recorded values have any influence of bronchodilation during the assessment. Bronchodilators can be used during diagnostic spirometry to determine if the patient's airflow limitation is reversible possibly indicating a diagnosis of asthma rather than or in addition to COPD; this is performed by measuring a patient's

baseline FEV_1 and FVC, administering a standardised dose of bronchodilator (such as salbutamol or ipratropium, or with a short course of oral prednisolone) and then repeating the measurement and assessing the changes between the two. A significant increase in the FEV_1, widely accepted to be both greater than 12% and greater than 200 millilitres, is considered to be 'reversible', however this cut-off is arbitrary and varies according to reference source (Pellegrino *et al.*, 2005).

Reversibility testing has been subject to controversy over the years due to some important limitations including a lack of reproducibility and a poor prediction of long term therapy response (Calverley, Burge*, et al.*, 2003; Tashkin *et al.*, 2003). Recommendations on how to best conduct and interpret spirometry results have differed in prevailing clinical guidelines and have changed over the years. The 2004 NICE COPD guideline made no reference to whether or how reversibility testing should be incorporated into diagnostic spirometry (National Institute for Health and Clinical Excellence, 2004): the 2010 update however clarified this and recommended that only a post-bronchodilator measurement of lung function should be utilised to confirm a diagnosis of COPD although a standard specification of what constitutes 'post-bronchodilator' was unable to be made (National Institute for Health and Clinical Excellence, 2010). The GOLD COPD guideline has consistently recommended the use of post-bronchodilator spirometry for the diagnosis of COPD. Versions of the guideline before and up to 2005 also recommended reversibility testing as a useful tool to rule out a diagnosis of asthma, establish a patient's best lung function, gauge prognosis or assess potential response to treatment (Global Initiative for Chronic Obstructive Lung Disease, 2005). However, this recommendation was dropped in later updates due to a lack of evidence. It is unclear whether spirometry values recorded in the FV database were pre- or post-bronchodilator values. Some of the FEV_1/FVC ratios greater than 0.7 may be the result of a positive response to a reversibility test. Other scenarios are possible, including patients on the register who are mis-diagnosed (although they may have asthma or restrictive lung disease), or mis-recorded of spirometric information in the medical record and subsequently, the FV database. These scenarios are also likely causative reasons underlying some of the unusual age trends within the KY database such as the large proportion of patients less than 40 years of age with insurance claims for COPD. This may have resulted from mis-coding of ICD-9 CM

codes in the KY database. Unfortunately, due to the limitations of retrospective analysis it is impossible to ascertain the full explanation.

The selective influence of Medicare on the age structure of the KY database has been noted previously but it is worth highlighting that this effect would be particularly pronounced for patients with COPD because of timeline of the disease in later life, with the database failing to capture an older cohort of patients who utilise Medicare for their primary or only healthcare coverage. The relative lack of patients with COPD over 60 years of age in the KY database suggests this is the most likely case. As such, the external validity of the KY database patients with COPD must be considered within this limited context, recognising that the database population is not comprehensive and conclusions should be extrapolated to the population-at-large with caution.

5.3 Medicine use trends

5.3.1 Methods

Analyses were conducted in a similar fashion to the analysis of patients with asthma, as described in section 4.3.1, with slight variations made to accommodate for differences between disease and treatment characteristics. Ipratropium, ipratropium/SABA combination inhalers and tiotropium were included as additional medicines in all analyses due to their specific licensing and use for the treatment of COPD and analyses for LTRAs were omitted. ICS were assessed cumulatively by therapeutic class as opposed to individual agent. Sub-analyses for children were also omitted and age groups within analyses were also adjusted, as described previously. Analysis of PDD was also omitted based on licensing considerations for medicines for the treatment of COPD which only are valid for a specific dose.

Additional analysis was conducted for both adherence and persistence to compare these metrics across both asthma and COPD diagnoses in the FV database. Patients who received maintenance medications (ICS, LABA, combination therapy inhalers, theophyllines or LAMA) during 2008 – 2009 were included. Two binary logistic regression models were utilised to separately assess predictors of adherence and persistence. For adherence the outcome of interest was achievement of an MPR of at least 80% therefore including both adequate supply and oversupply; this binary measure was chosen over a continuous measure since oversupply does not confer any demonstrable therapeutic benefit over adequate supply. For persistence, consideration of the descriptive Kaplan-Meier results suggested a non-proportionality of hazards over time; therefore, logistic regression with an outcome of interest of persistence past 100 days of therapy was utilised over a Cox regression analysis. For both regressions, patient- and treatment-related variables of interest (age, sex, diagnosis, therapeutic class of medication) were assessed first in univariable fashion; SABA and OCS utilisation (doses/day and receipt [yes/no], respectively) during the study period were also entered in the adherence model to include a measure of disease control and classification of treatment as new/established therapy was utilised in the persistence model. Patients were considered to be on ‘new’ therapy if they had no history of being prescribed an agent in the specified therapeutic class in the six months prior to the start of the study period. Significant variables from the univariable analysis were filtered into the

final forward stepwise multivariable models with α set at 0.05 for entry and 0.10 for removal. Results were reported with odds ratios and 95% confidence intervals. Model fit was assessed using the c-statistic.

5.3.2 Results

5.3.2.1 Prescription volume

A total of 5,159 patients with COPD in the FV database received 223,305 prescriptions relating to their care from 2007 – 2009 (Table 5.4(a)). Prescription volume in the database increased from levels in 2007 and largely stabilised in 2008 and 2009. Despite differing volumes, intra-class preferences remained similar to those in asthma (salbutamol vs. terbutaline, salmeterol vs. formoterol); whereas the volume differential between Seretide® (fluticasone/salmeterol) and Symbicort® (budesonide/formoterol) was 3-fold for patients with asthma, it was nearly 9-fold for patients with COPD. Tiotropium was the most widely utilised maintenance treatment among therapies assessed.

Table 5.4a: Prescription volume of selected medicines for patients with COPD (2007 – 2009) in the FV database

Medicine	Prescriptions (patients), n		
	2007	2008	2009
Salbutamol	24,601 (3,185)	23,499 (3,745)	22,709 (3,767)
Terbutaline	1,308 (205)	1,131 (218)	976 (202)
Ipratropium	2,016 (263)	1,725 (276)	1,235 (205)
Ipratropium/salbutamol	4,281 (480)	2,709 (444)	1,647 (239)
ICS (all)	6,525 (1,033)	5,356 (1,039)	3,539 (763)
Seretide® (fluticasone/salmeterol)	14,083 (1,749)	14,117 (2,161)	14,333 (2,299)
Symbicort® (budesonide/formoterol)	1,340 (186)	1,547 (243)	1,736 (283)
Salmeterol	2,537 (346)	2,025 (369)	1,758 (381)
Formoterol	132 (22)	130 (24)	91 (18)
Tiotropium	15,233 (2,114)	15,689 (2,630)	16,433 (2,878)
Theophylline	2,553 (292)	2,349 (335)	2,153 (316)
Prednisolone	2,736 (846)	4,486 (1,352)	4,587 (1,430)
Total	**77,345 (4,026)**	**74,763 (4,428)**	**71,197 (4,430)**

A total of 19,519 prescriptions were dispensed to 2,138 patients with COPD in the KY database from 2007 – 2009 with relatively stable volume across the three years assessed (Table 5.4(b)). Ipratropium-containing inhalers (both single-agent and in combination with albuterol) were utilised frequently. Combination therapy inhalers were the most utilised maintenance therapy for COPD in the KY database.

Table 5.4b: Prescription volume of selected medicines for patients with COPD (2007 – 2009) in the KY database

Medicine	Prescriptions (patients), n		
	2007	2008	2009
Albuterol	1,743 (608)	1,628 (624)	165 (629)
Pirbuterol	41 (14)	31 (13)	19 (5)
Levalbuterol	285 (102)	349 (112)	326 (94)
Ipratropium	207 (64)	164 (67)	172 (66)
Ipratropium/albuterol	717 (220)	671 (234)	633 (221)
ICS (all)	564 (157)	474 (150)	382 (120)
Advair® (fluticasone/salmeterol)	1,352 (365)	1,228 (352)	1,285 (330)
Symbicort® (budesonide/formoterol)	44 (15)	220 (74)	409 (141)
Salmeterol	71 (15)	32 (12)	17 (6)
Formoterol	177 (43)	150 (35)	73 (24)
Tiotropium	1,115 (239)	1,189 (266)	1276 (279)
Theophylline	326 (56)	261 (45)	232 (35)
Prednisone	1,070 (473)	1,182 (555)	1,148 (565)
Total	**6,618 (1,083)**	**6,407 (1,174)**	**6,494 (1,118)**

5.3.2.2 Defined daily dose

In the FV database, the utilisation of SABA (salbutamol and terbutaline) among patients with COPD decreased 25.0% over the three-year period with a high of 1,070 DDDs in February 2007 and a low of 757 DDDs in October 2009 (Figure 5.8). On the other hand, SABA utilisation (albuterol, pirbuterol and levalbuterol) in the KY database increased 29.2% during the same period with a low of 167 DDDs in January 2009 and a high of 315 DDDs in December 2009. Despite this increase, the overall magnitude of utilisation of SABA therapy in the KY database was approximately one-third that of the FV database.

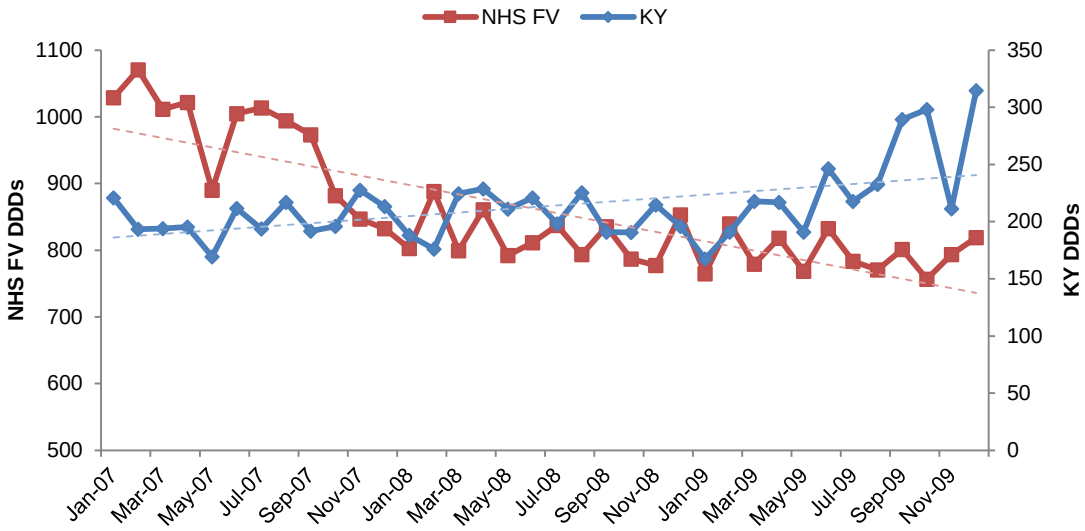


Figure 5.8: DDDs per 1,000 patients with COPD per day for SABAs in the FV and KY databases (2007 – 2009)

For single-agent ipratropium inhalers, use in the FV database had a steady decrease of 58.1%, from a high of 141 DDDs in January 2007 to a low of 56 DDDs in August 2009 (Figure 5.9). The use of combination ipratropium/salbutamol inhalers was approximately two-fold higher but decreased by 89.1% from a high of 351 DDDs in February 2007 to 82 DDDs in October 2009: while decreasing steadily from 2007 – 2008 the trend began to level out in 2009 (Figure 5.10). For the KY database, single-agent ipratropium utilisation increased 33.7%, with a low of 15 DDDs in November 2008 and a high of 82 DDDs in December 2007. For combination ipratropium/albuterol utilisation a decrease of 39.0% occurred over the three years with a maximum of 206 DDDs in December 2007 and a minimum of 85 DDDs in February 2009. Combination bronchodilator therapy was also preferred in the KY database by 3- to 4-fold, although this margin closed in later years as the use of single agent ipratropium increased.

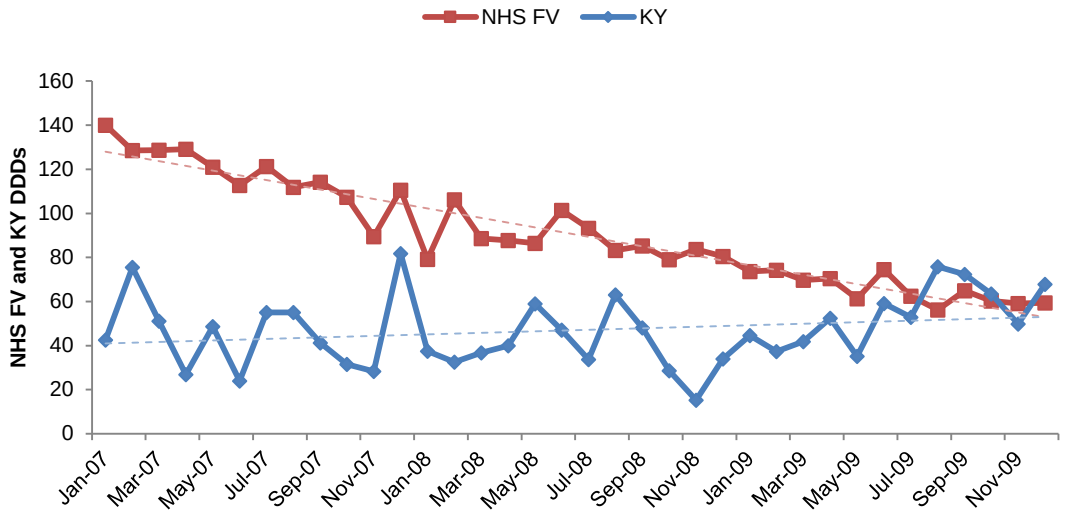


Figure 5.9: DDDs per 1,000 patients with COPD per day for ipratropium in the FV and KY databases (2007 – 2009)

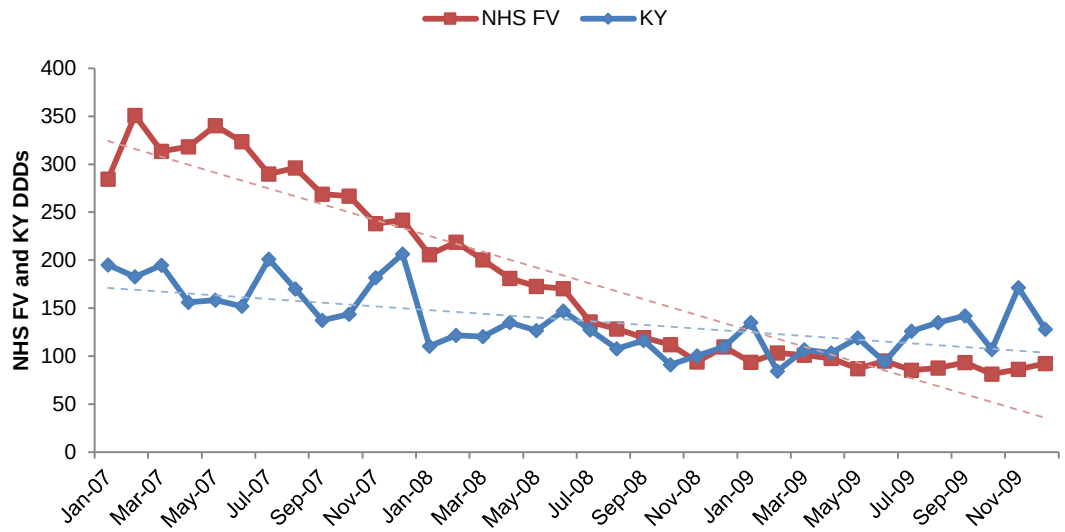


Figure 5.10: DDDs per 1,000 patients with COPD per day for ipratropium/albuterol in the FV and KY databases (2007 – 2009)

Among total ICS products in the FV database (including beclometasone, budesonide, and fluticasone formulations) utilisation sharply decreased by 66.8% with a high of 396 DDDs in February 2007 and a low of 132 DDDs in October 2009 (Figure 5.11). Utilisation similarly decreased in the KY database, although to a lesser degree of 38.3%, with a high of 70 DDDs in March 2007 and a low of 31 DDDs in February 2008. The magnitude of utilisation was approximately 5-fold higher in the FV database across all time points.

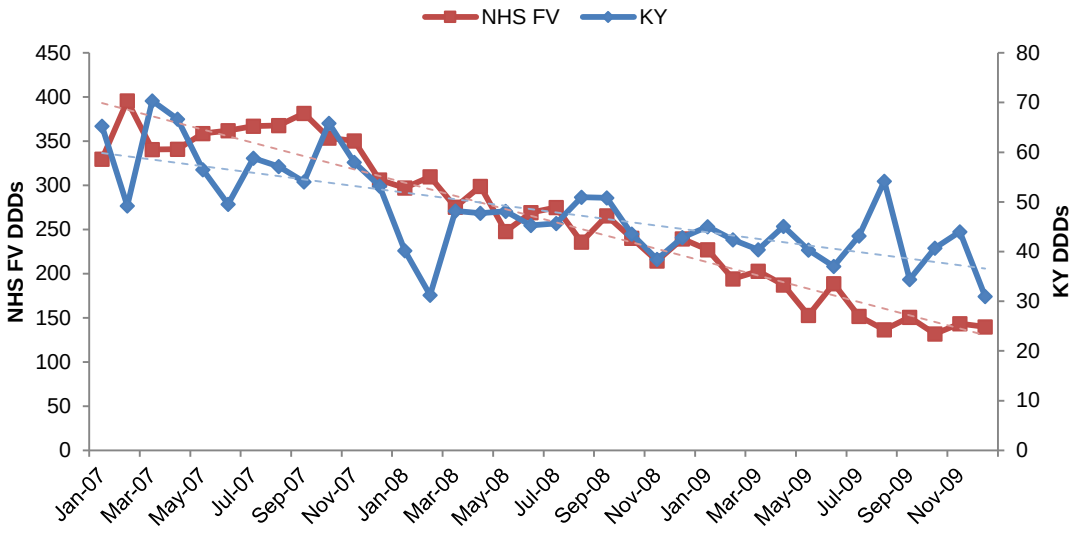


Figure 5.11: DDDs per 1,000 patients with COPD per day for total ICS in the FV and KY databases (2007 – 2009)

For LABA inhalers, utilisation decreased 50.0% and 78.1% in the FV and KY databases, respectively (Figure 5.12). Values in the FV database ranged from 133 DDDs in April 2007 to 63 DDDs in January 2009; values in the KY database ranged from 52 DDDs in August 2007 to 6 DDDs in March 2009.

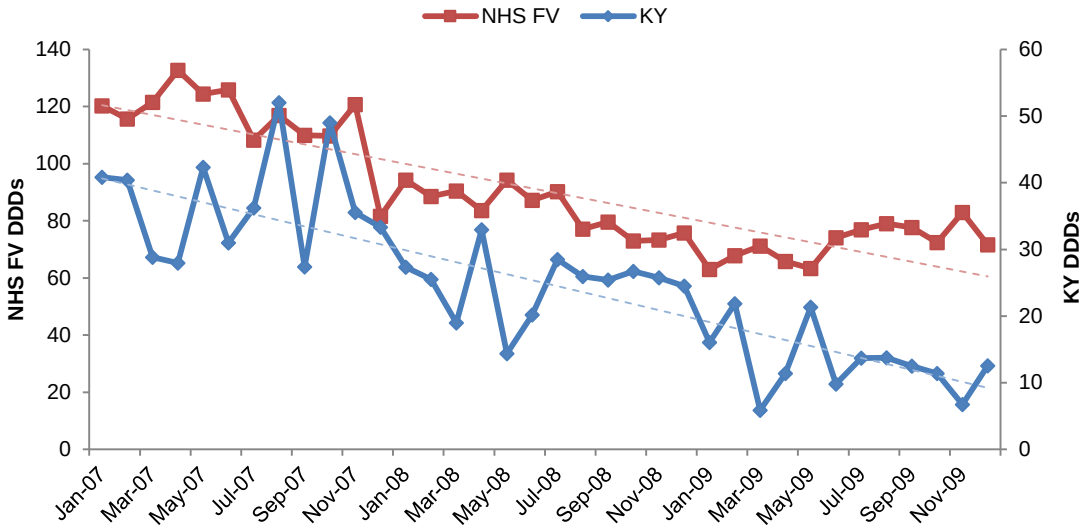


Figure 5.12: DDDs per 1,000 patients with COPD per day for total LABA in the FV and KY databases (2007 – 2009)

For combination inhalers, utilisation for both fluticasone/salmeterol and budesonide/formoterol in the FV database was relatively stable with a 10.4% decrease and 0.4% increase, respectively (Figures 5.13 and 5.14). Utilisation

ranged from 701 DDDs in February 2007 to 493 DDDs in December 2007 for fluticasone/salmeterol, and 42 DDDs in May 2008 to 57 DDDs in February 2009 for budesonide/formoterol. Utilisation for fluticasone/salmeterol in the KY database was also relatively stable with a 4.7% decrease, ranging from 154 DDDs in June 2008 to 225 DDDs in August 2009. However, the use of budesonide/formoterol was seen for the first time during July 2007 rising to a high of 72 DDDs in October 2009.

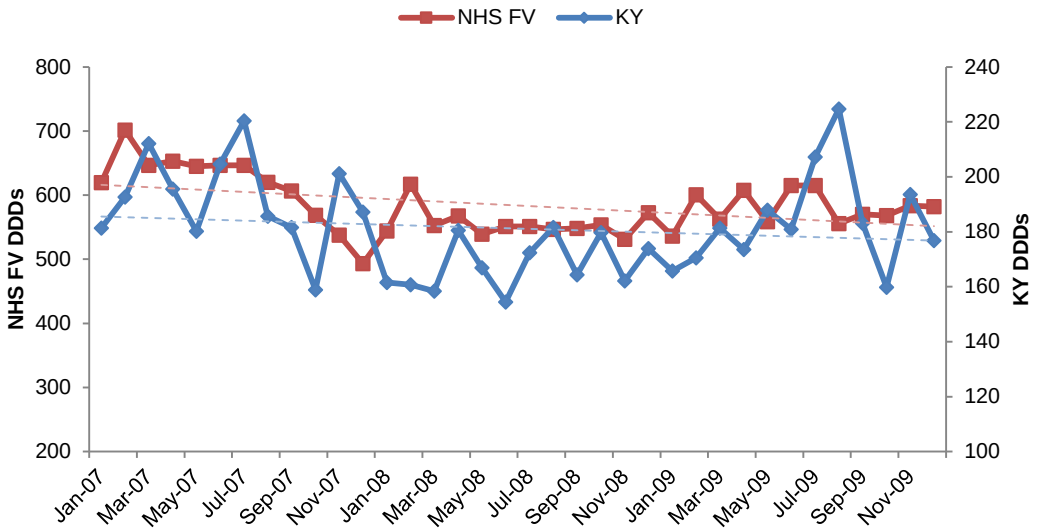


Figure 5.13: DDDs per 1,000 patients with COPD per day for fluticasone/salmeterol in the FV and KY databases (2007 – 2009)

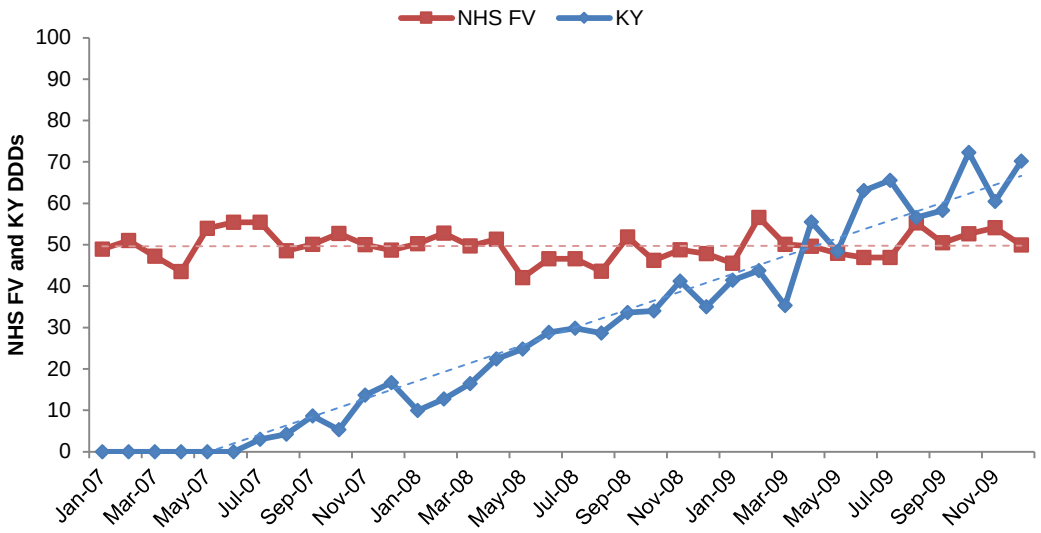


Figure 5.14: DDDs per 1,000 patients with COPD per day for budesonide/formoterol in the FV and KY databases (2007 – 2009)

Tiotropium use was overall stable in the FV database with a 1.3% increase over the time period ranging from 642 DDDs in December 2007 to 782 DDDs in December 2009; utilisation fluctuated from a decreasing trend in 2007 to stabilisation in 2008 and subsequent increase in 2009 (Figure 5.15). In the KY database, utilisation was on the increase at 42.4% but at less than a quarter of the use in the FV database from a low of 102 DDDs in January 2007 to a high of 213 DDDs in August 2009.

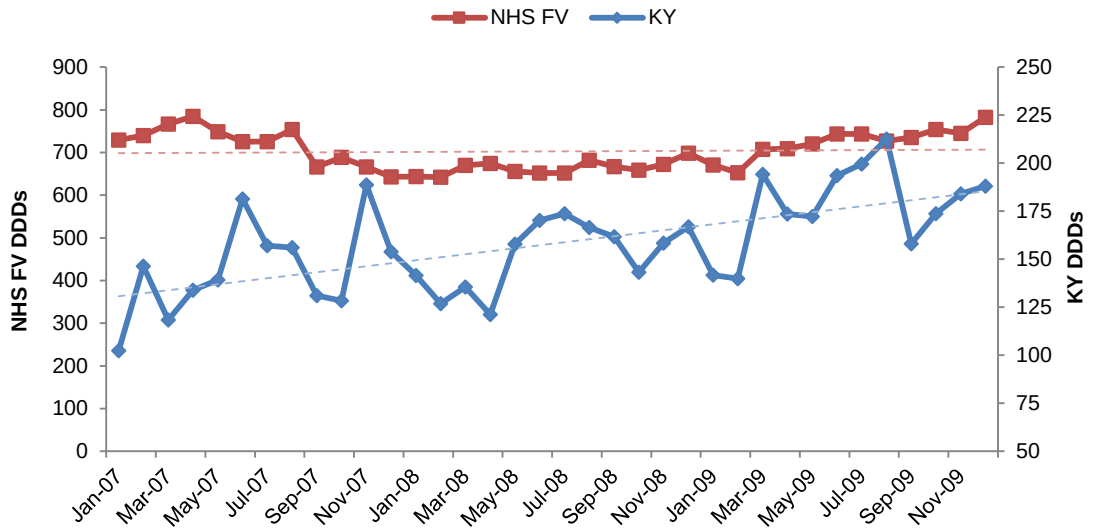


Figure 5.15: DDDs per 1,000 patients with COPD per day for tiotropium in the FV and KY databases (2007 – 2009)

Theophyllines were utilised approximately twice as much in the FV database compared to the KY database although both were subject to decreasing use overall at 38.7% and 44.3%, respectively (Figure 5.16). Use in the FV database ranged from 190 DDDs in January 2007 to 93 DDDs in January 2009 and use in the KY database ranged from 80 DDDs in January 2007 to 32 DDDs in July 2008.

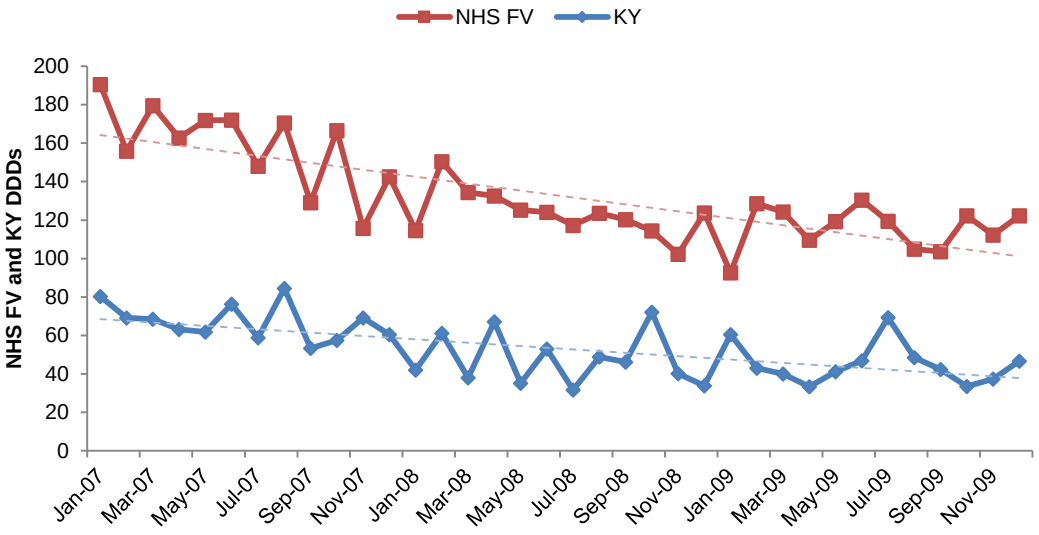


Figure 5.16: DDDs per 1,000 patients with COPD per day for theophylline in the FV and KY databases (2007 – 2009)

The use of OCS (prednisolone in the FV database and prednisone in the KY database) was increasing although to a greater degree in the FV database (104.6%) compared to the KY database (12.8%) (Figure 5.17). Values in the FV database ranged from 48 DDDs in May 2007 to 177 DDDs in December 2008 and values in the KY database ranged from 97 DDDs in October 2007 to 174 DDDs in November 2007.

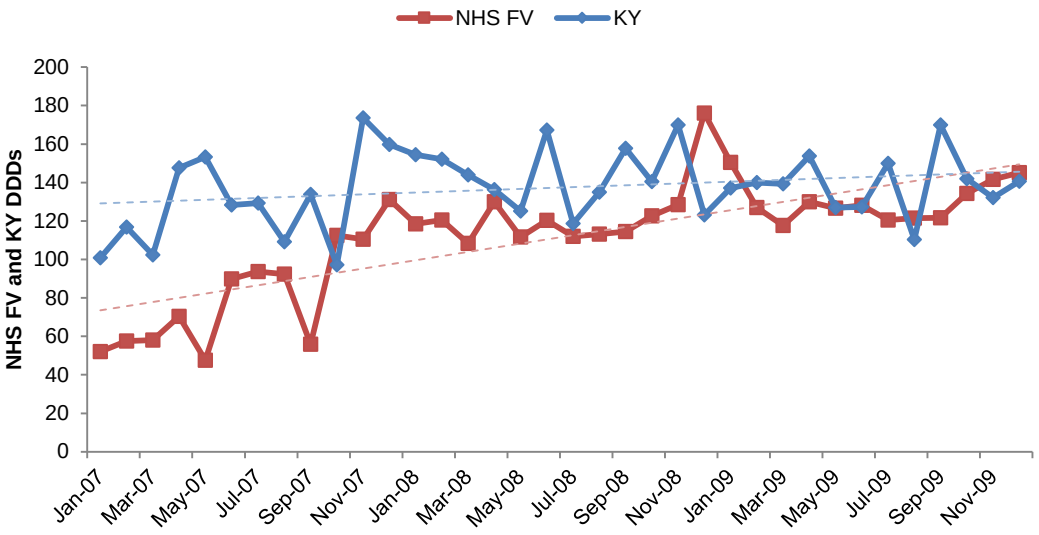


Figure 5.17: DDDs per 1,000 patients with COPD per day for OCS in the FV and KY databases (2007 – 2009)

5.3.2.3 Adherence

Descriptive analysis

A total of 6,506 episodes of maintenance medicine use among 3,576 patients were evaluated in the FV database with a median medication possession ratio (MPR) of 95.6% (IQR: 66.2 to 118.0%); median MPR was similar between men and women (94.9 vs. 96.1%, p=0.904). Overall, 42.0% of MPRs were classified as an adequate supply with a remaining 23.8% as undersupply and 34.2% as oversupply. Of the patients included 1,345 (37.6%) were treated with a single therapeutic class and a further 1,636 (45.7%) patients with two classes. Five hundred and eighty-six episodes of chronic medicine use were evaluated for 417 patients in the KY database. The median MPR was 71.5% (IQR: 42.8 to 93.2%) and was similar between men and women (75.0 vs. 70.4%, p=0.09). MPR classification resulted in the majority of episodes (59.2%) classified as undersupply. Adequate supply accounted for 38.6% of episodes, with the small remainder (2.2%) as oversupply. A total of 280 patients (67.1%) patients were treated with a single therapeutic class.

Adherence generally had a positive correlation with age in the FV database, ranging from a median MPR of 90.5% (IQR: 47.3 to 123.5%) for patients less than 40 years of age to 97.5% (IQR: 55.7 to 113.6%) for patients greater than 90 years of age. Terminal age categories contained relatively small numbers of patients when stratified across MPR classifications and were therefore interpreted cautiously within the trend (Table 5.5(a)). Adequate supply increased from a low of 32.1% for patients aged 40 to 49 years old to a high of 44.6% for patients aged 70 to 79 years old. Undersupply was generally more common for younger patients at 38.9% among patients 40 to 49 years old.

Table 5.5a: Medication supply by MPR classification for patients with COPD by age group (2007 – 2009) in the FV database

Age (years)	Undersupply n (%)	Adequate supply n (%)	Oversupply n (%)
< 40	10 (40.0)	9 (36.0)	6 (24.0)
40-49	98 (38.9)	81 (32.1)	73 (29.0)
50-59	349 (35.7)	371 (37.9)	259 (26.4)
60-69	719 (34.2)	884 (42.0)	501 (23.8)
70-79	746 (33.1)	1,005 (44.6)	505 (22.4)
80-89	287 (33.8)	365 (43.0)	196 (23.1)
≥ 90	18 (42.9)	16 (38.1)	8 (19.1)

In the KY database, sample size limited the analysis but the proportion of patients with an adequate supply of medication increased with age from a low of 24.6% among patients 40 to 49 years old to 61.8% among patients 80 to 89 years old (Table 5.5(b)). Oversupply was very infrequent and without notable trend.

Table 5.5b: Medication supply by MPR classification for patients with COPD by age group (2007 – 2009) in the KY database

Age (years)	Undersupply n (%)	Adequate supply n (%)	Oversupply n (%)
< 40	6 (66.7)	3 (33.3)	0 (0.0)
40-49	49 (75.4)	16 (24.6)	0 (0.0)
50-59	141 (62.7)	81 (36.0)	3 (1.3)
60-69	106 (54.4)	81 (41.5)	8 (4.1)
70-79	33 (56.9)	24 (41.4)	1 (1.7)
80-89	12 (35.3)	21 (61.8)	1 (2.9)
≥ 90	0 (0.0)	0 (0.0)	0 (0.0)

Among all therapeutic classes in the FV database, theophylline had the highest median MPR at 103.2% (IQR: 92.3 to 129.7%) as well as the highest proportion of MPRs classified with an adequate supply (Table 5.6(a)). Among inhaled therapies ICS had the highest median MPR at 98.0% (IQR: 60.3 to 143.5%) but this was largely influenced by a high proportion of oversupply (34.2%) rather than adequate supply which was lowest among all therapies; LAMA had the highest proportion of adequate supply at 47.7%. Undersupply was the least for theophylline and highest for LABA inhalers.

Table 5.6a: Medication supply by MPR classification for patients with COPD by therapeutic class (2007 – 2009) in the FV database

Therapeutic class	Undersupply n (%)	Adequate supply n (%)	Oversupply n (%)
ICS	329 (36.8)	259 (29.0)	305 (34.2)
LABA	178 (42.3)	142 (33.7)	101 (24.0)
CMB	849 (38.3)	892 (40.3)	475 (21.4)
TP	40 (14.0)	156 (54.5)	90 (31.5)
LAMA	831 (30.9)	1,282 (47.7)	577 (21.5)

In the KY database, theophyllines also had the highest overall median MPR at 90.9% (IQR: 71.4 to 98.7%) and LAMA had the highest among inhaled therapies at 77.9% (IQR: 48.6 to 95.2%). Similar trends were noted among the categorical classification of MPR, with the exception of LABA therapy, which had a slightly higher proportion of patients with adequate supply (46.2%) compared to LAMA therapy (45.9%) (Table 5.6(b)).

Table 5.6b: Medication supply by MPR classification for patients with COPD by therapeutic class (2007 – 2009) in the KY database

Therapeutic class	Undersupply n (%)	Adequate supply n (%)	Oversupply n (%)
ICS	46 (74.2)	14 (22.6)	2 (3.2)
LABA	14 (53.8)	12 (46.2)	0 (0.0)
CMB	149 (66.5)	68 (30.4)	7 (3.1)
TP	15 (36.6)	25 (61.0)	1 (2.4)
LAMA	123 (52.8)	107 (45.9)	3 (1.3)

A total of 89.3% of medicine use episodes for COPD in the FV database were accompanied by treatment with a SABA at a median of 3.6 doses/day (IQR: 1.7 to 7.0 doses/day). The use of SABA was highest among those with an oversupply of maintenance medication at 6.0 doses/day (IQR: 3.0 to 9.9 doses/day) decreasing to 3.7 doses/day (IQR: 1.8 to 6.9 doses/day) for adequate supply and 2.5 doses/day (IQR: 1.3 to 4.7 doses/day) for undersupply. Only 44.2% of episodes in the KY database had administered with concurrent SABA treatment at a median of 2.1 doses/day (IQR: 0.8 to 4.6 doses/day). The amount of SABA prescribed was similar between undersupply at 2.0 doses/day (IQR: 0.8 to 4.1 doses/day) and adequate supply at 2.3 doses/day (IQR: 0.7 to 5.2 doses/day, p=0.516 for comparison)

Regression analysis

In the regression analysing adherence both male sex and increasing age were associated with higher odds of achieving an MPR of at least 80% (Table 5.7). Both a diagnosis of COPD and treatment with theophyllines or LAMA were associated with higher odds of the outcome although these effects were comparatively softened on transition to the multivariable analysis. The number of doses/day of SABA prescribed during the study period increased alongside MPR with each additional dose/day correlating to an 11% increase in the odds of achieving an adequate MPR: receiving a prescription for OCS was also associated with an increased odds of an adequate MPR although this effect failed to meet significance for inclusion in the multivariable model. The overall fit of the model as assessed by the c-statistic (0.69) was modest.

Table 5.7: Multivariable logistic regression for medication adherence in the FV database (2008 – 2009)
† *univariable analysis with MPR ≥ 80% utilised as outcome*
‡ *multivariable analysis adjusted by sex, age, diagnosis, therapeutic class and SABA utilisation, with MPR ≥ 80% utilised as outcome*
§ *model fit assessed by c-statistic: 0.69 (95% CI: 0.68-0.70)*

Variable	Crude OR (95% CI) †	Adjusted OR (95% CI) ‡§	Adjusted OR p-value
Sex			
Female	1 (reference)	1 (reference)	0.024
Male	1.15 (1.09 – 1.22)	1.08 (1.01 – 1.14)	
Age (years)			
< 20	1 (reference)	1 (reference)	<0.001
20-39	1.08 (0.97 – 1.21)	0.97 (0.86 – 1.09)	
40-59	1.40 (1.27 – 1.54)	1.19 (1.07 – 1.32)	
60-79	2.14 (1.95 – 2.36)	1.57 (1.40 – 1.76)	
≥ 80	2.36 (2.04 – 2.73)	1.66 (1.41 – 1.96)	
Diagnosis			
Asthma	1 (reference)	1 (reference)	<0.001
COPD	2.15 (2.03 – 2.29)	1.27 (1.15 – 1.40)	
Therapeutic class			
ICS	1 (reference)	1 (reference)	<0.001
LABA	0.79 (0.69 – 0.90)	0.63 (0.55 – 0.73)	
CMB	1.02 (0.95 – 1.10)	0.86 (0.79 – 0.92)	
TP	2.36 (2.14 – 2.60)	1.46 (1.29 – 1.66)	
LAMA	2.22 (2.01 – 2.46)	1.38 (1.21 – 1.57)	
SABA (doses/day)	1.11 (1.10 – 1.12)	1.11 (1.10 – 1.12)	<0.001
OCS			
No	1 (reference)	N/A	0.971
Yes	1.25 (1.18 – 1.33)		

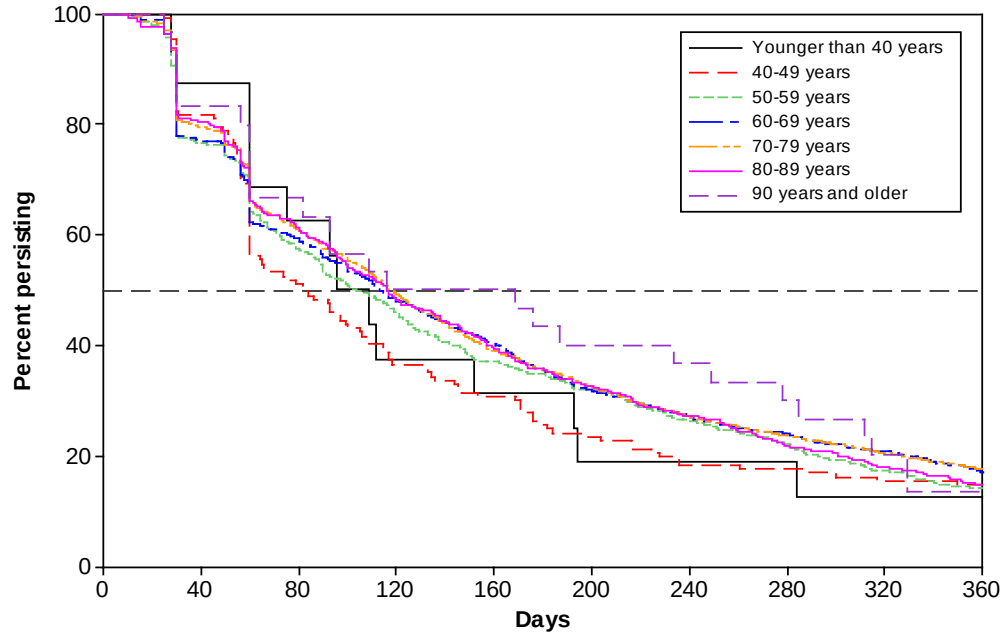
CI: confidence interval; CMB: combination therapy inhaler; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroid; OR: odds ratio; SABA: short-acting beta agonist; TP: theophylline

5.3.2.4 Persistence

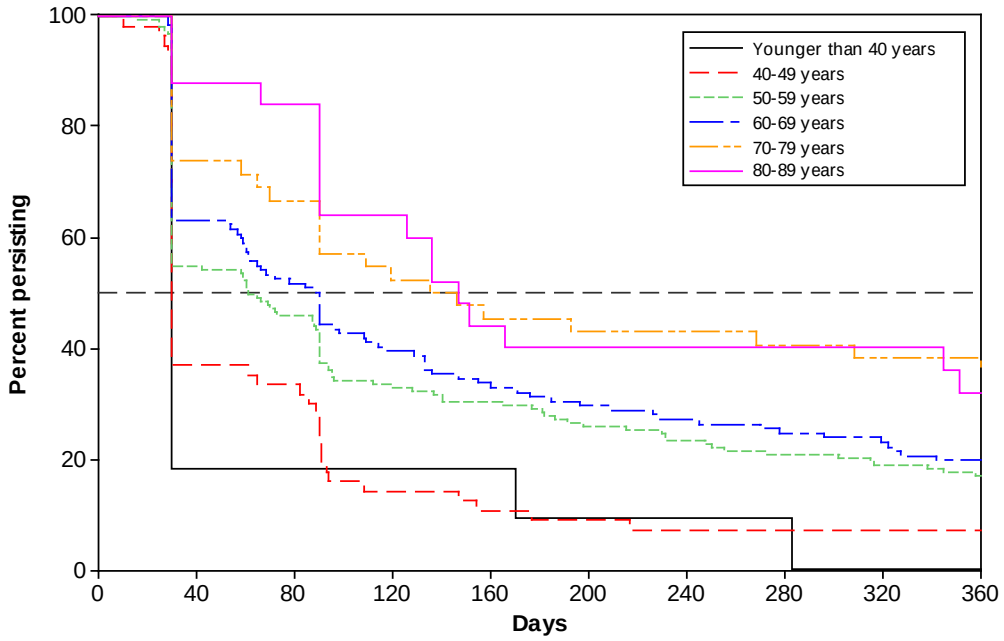
Descriptive analysis

A total of 4,378 episodes of medicine use were evaluated for persistence in the FV database with an overall mean and median time to discontinuation (TTD) of 236 days (95% CI: 228 to 245 days) and 114 days (IQR: 54 to 259 days), respectively. A total of 16% of patients overall were found to be persistent with therapy after one year. Men had a higher median duration of persistence at 120 days compared to 108 days for women (p=0.039). In the KY database, 412 episodes were assessed for persistence resulting in an overall mean TTD of 211 days (95% CI: 184 to 237 days) and a median TTD of 72 days (IQR: 30 to 231 days): 19% of patients were persistent after one year.

The relationship of persistence with age was variable but in general showed a longer TDD among older patients (Figure 5.18(a) and (b)). In the FV database, the median TTD ranged from 84 days (IQR: 55 to 182 days) for patients aged 40 to 50 years old to 118 days (IQR: 56 to 261 days) for patients aged 70 to 80 years old. Despite separation of the Kaplan-Meier curves throughout the year, at the end of the year most had converged ranging from 13% (for less than 40 years of age) to 17% (for 70 to 80 years of age). For the KY database, this relationship was largely more variable, as a function of sample size, but generally held true from a median TTD of 30 days for patients both aged less than 40 years and 40 to 49 years of age to 147 days (IQR: 90 to 365 days) for patients aged 80 to 90 years old. The Kaplan-Meier curves were marked by significant drop-offs early in therapy signifying a single prescription with no follow-up fill for the medication. This drop-off was where separation of age trends was most apparent.



(a)

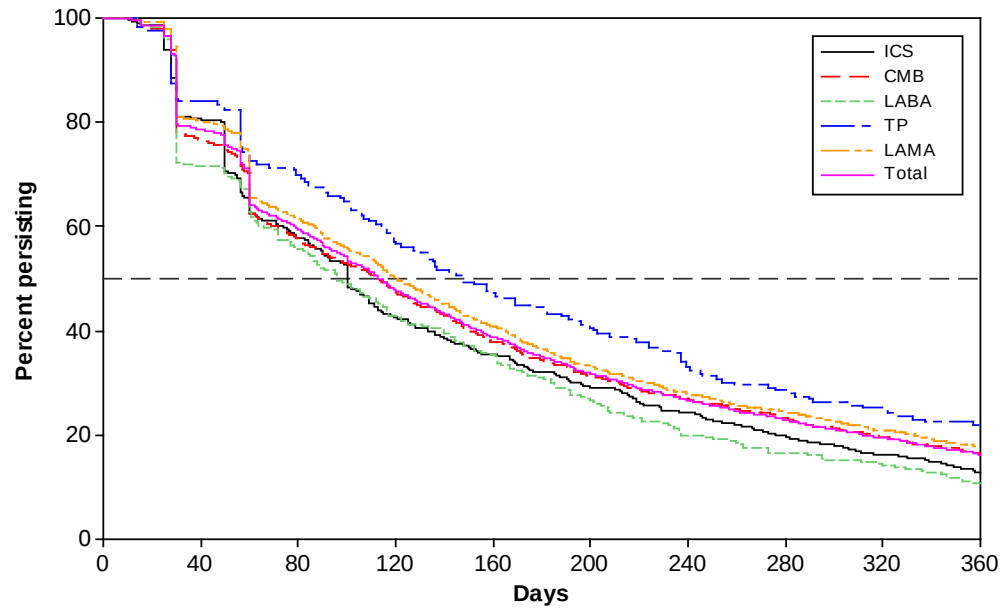


(b)

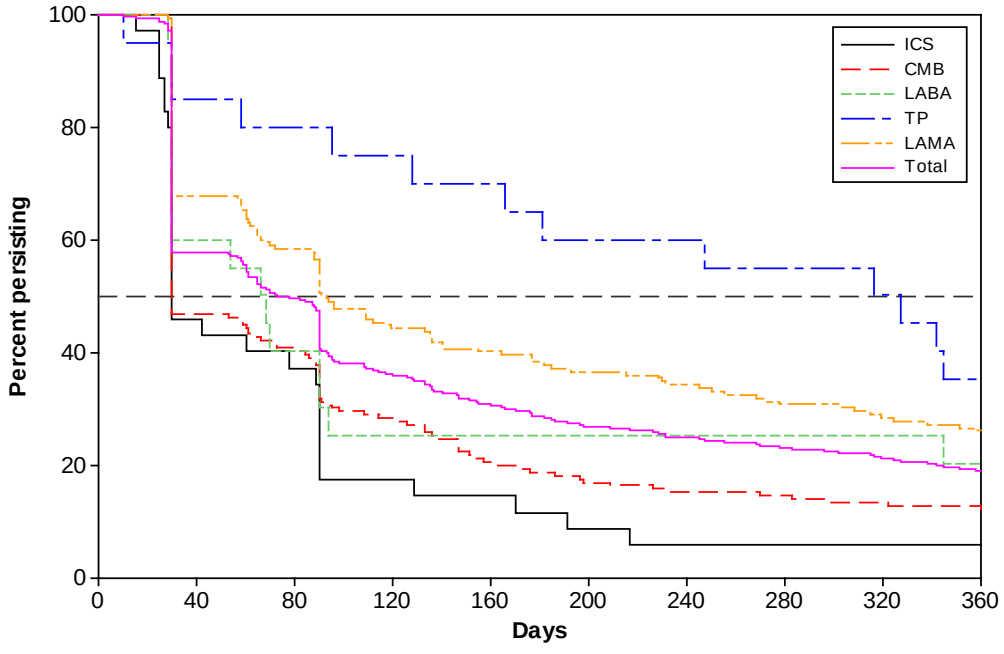
Figure 5.18: Persistence curve for patients with COPD by age (2008) in the **(a)** FV database and **(b)** KY database

Similar to adherence, persistence was greatest for theophyllines among therapeutic classes with a median TTD of 147 days (IQR: 57 to 320 days) and 21% of patients persisting at one year in the FV database (Figure 5.19(a)). LAMA therapy had the highest median TTD among inhaled therapies at 121 days (IQR: 58 to 272 days) and 17% of patients persisting at one year. In the KY database, persistence was

also greatest for theophyllines at a median TTD of 316 days (IQR: 95 to 365 days) and 35% of people persisting at one year (Figure 5.19(b)). The highest persistence for inhaled therapy was for LAMAs at 91 days (IQR: 30 to 365 days) and 26% of patients persisting at one year.



(a)



(b)

Figure 5.19: Persistence curve for patients with COPD by therapeutic class (2008) in the **(a)** FV database and **(b)** KY database

Regression analysis

For persistence male sex and increasing age were again positively associated with the outcome (Table 5.8). Diagnosis with COPD, although significant on a univariable level, failed to meet significance for inclusion in the final model. Therapy with theophylline was associated with higher odds of persisting past 100 days of therapy, but LAMA failed to meet this criterion in the final model as well. Newly initiated therapy was associated with 21% lower odds of persisting past 100 days compared to patients on already established therapy. The fit of the model was relatively poor as shown by the c-statistic value of 0.58.

Table 5.8: Multivariable logistic regression for medication persistence in the FV database (2008 – 2009)
† *univariable analysis with persistence > 100 days utilised as outcome*
‡ *multivariable analysis adjusted by sex, age, therapeutic class and type of therapy, with persistence > 100 days utilised as outcome*
§ *model fit assessed by c-statistic: 0.58 (95% CI: 0.57 – 0.59)*

Variable	Crude OR (95% CI) †	Adjusted OR (95% CI) ‡§	Adjusted OR p-value
Sex			
Female	1 (reference)	1 (reference)	<0.001
Male	1.14 (1.07 – 1.21)	1.14 (1.07 – 1.21)	
Age (years)			
< 20	1 (reference)	1 (reference)	<0.001
20-39	0.92 (0.83 – 1.02)	0.97 (0.88 – 1.08)	
40-59	1.11 (1.01 – 1.22)	1.17 (1.06 – 1.29)	
60-79	1.52 (1.38 – 1.67)	1.58 (1.43 – 1.75)	
≥ 80	1.61 (1.38 – 1.88)	1.66 (1.41 – 1.95)	
Diagnosis			
Asthma	1 (reference)	N/A	0.739
COPD	1.32 (1.23 – 1.41)		
Therapeutic class			
ICS	1 (reference)	1 (reference)	<0.001
LABA	0.66 (0.58 – 0.74)	0.60 (0.53 – 0.68)	
CMB	0.89 (0.83 – 0.95)	0.81 (0.76 – 0.88)	
TP	1.96 (1.57 – 2.45)	1.65 (1.31 – 2.06)	
LAMA	1.23 (1.11 – 1.37)	0.94 (0.84 – 1.06)	
Type of therapy			
Established	1 (reference)	1 (reference)	<0.001
New	0.76 (0.71 – 0.82)	0.79 (0.73 – 0.85)	

CI: confidence interval; CMB: combination therapy inhaler; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroid; OR: odds ratio; TP: theophylline

5.3.3 Discussion

Tiotropium was the most utilised medicine for the treatment of COPD in the FV database but combination therapy inhalers remained most used in the KY database, despite large increases in the utilisation of tiotropium over the time frame studied. Tiotropium was introduced to the UK market in 2002 approximately 2 years prior to introduction on the USA market. Guideline recommendations for tiotropium were first included in the 2003 GOLD update and have featured ever since this time. This initial inclusion recommended tiotropium as the preferred treatment over short-acting bronchodilators for patients with moderate to very severe COPD (Global Initiative for Chronic Obstructive Lung Disease, 2003). Tiotropium similarly first featured in the 2004 NICE COPD guideline and the joint 2004 ATS-ERS COPD guideline although with less definitive recommendations for its place in therapy (American Thoracic Society *et al.*, 2004; National Institute for Health and Clinical Excellence, 2004). Further studies have consolidated the place of tiotropium as a first-line maintenance therapy based on improvements in lung function, quality of life, rate of exacerbations and mortality (Celli *et al.*, 2009; Tashkin *et al.*, 2008). In addition to the clinical evidence the once-daily dosing regimen provides an advantage above other agents utilised for the treatment of COPD. In more recent practice ICS, as a part of combination therapy, has been proposed as more effective in reducing the risk of COPD exacerbations and therefore are recommended over bronchodilators alone in patients who are 'frequent exacerbators' (Kardos *et al.*, 2007). Higher utilisation of combination therapy may then result from more patients being 'frequent exacerbators' and this can be partially supported by the higher utilisation of OCS in the KY database. However, only one trial to date has evaluated the difference in exacerbation prevention among patients treated with combination therapy or tiotropium and it found no difference between therapies (Wedzicha *et al.*, 2008). The GOLD guideline consequently recommends either therapy as initial treatment for Group C patients (those with limited symptoms but high exacerbation risk or advanced airflow limitation) (Global Initiative for Chronic Obstructive Lung Disease, 2013). The preference for combination therapy among a COPD population is unclear.

Of additional interest in utilisation trends is the comparison of patients with COPD against those patients with asthma (section 4.3.3). Both diseases utilise similar

therapies for both reliever and maintenance treatment (albeit with different criteria) and within the same health board or commercial insurance provider are subject to similar changes in formulary preferences that might alter utilisation. Therefore, differences in utilisation trends between patients with asthma and COPD are likely to be largely disease-driven. For instance, the use of SABA in the KY database decreased by 17.1% among patients with asthma but increased by 29.2% among patients with COPD. Utilisation of almost all reliever and maintenance therapies in the KY database for both asthma and COPD showed decreasing trends over time making the increasing SABA trend in COPD particularly noteworthy especially when considered in concert with the increasing trend of ipratropium in COPD. High utilisation of reliever therapy has a clear relationship with, and therefore may serve as a proxy for, secondary outcomes such as hospitalisations in asthma (Mudd *et al.*, 2006; Silver *et al.*, 2011) but this relationship has not been well evaluated in COPD. However, it remains possible that the increasing trend of reliever therapy in this analysis is a function of worsening disease symptomology over time, or poor adherence with maintenance medication for long-term disease control.

Budesonide/formoterol was initially approved by the FDA in July 2006, with a sole indication for asthma. Utilisation of the medication in the KY database was seen beginning in mid-2007 (presumably following the addition of the product to the third-party insurance formulary) for both patients with asthma and COPD. Despite the fact that the medication did not receive an indication for COPD until February 2009, it was used off-label for approximately two years. Greater increases occurred among patients with COPD which reached a high of 72 DDDs per 1,000 patients compared to asthma at 40 DDDs per 1,000 patients. Although fluticasone/salmeterol remained the most frequent choice for combination therapy for both asthma and COPD the greater market share of budesonide/formoterol in COPD may be the result of formulation considerations.

The majority of prescribing of fluticasone/salmeterol in either asthma or COPD in the USA is for Advair Diskus®, a DPI formulation, as opposed to Advair HFA®, a pMDI formulation, likely due to a manufacturer marketing push for the DPI formulation. Key aspects of the Advair® patent began to expire in 2010 – patent expiry occurs in stages due to separate patents on the medicine and device components of the formulation – but Advair Diskus® in particular continues to enjoy market exclusivity

because of the difficulties associated with developing a bioequivalent generic DPI formulations. To prove bioequivalence to a DPI formulation the manufacturer must show the generic formulation to be similar on a number of levels including same device/formulation, equivalent *in vitro* performance, equivalent systemic exposure, and equivalent local delivery (Lee, 2011). The cost and time barriers for generic DPI development have been high and preventative to prove full bioequivalence. Only recently has the FDA addressed this issue and released draft guidance on generic development for fluticasone/salmeterol products (Food and Drug Administration, 2013a). With continued exclusivity on both Advair Diskus® and Advair HFA®, the marketing push has focused on the former and costlier formulation.

Symbicort® was introduced to the USA market as a pMDI inhaler unlike the remainder of the world where it exists as a DPI inhaler. Although pMDIs can be more difficult to utilise by some patients due to the need for proper dexterity and hand-breath coordination they do provide some key benefits over DPIs. pMDIs are generally associated with a lower acquisition cost which can be preferable within the USA consumer and insurance market and also do not require a minimum level of inspiratory effort for full dose delivery (Chrystyn, 2007). Particularly in patients with COPD where the ability to produce a deep and forceful inhalation may be limited the use of a pMDI with or without the aid of a spacer may be preferable. The introduction of Symbicort® to the USA market was met with much enthusiasm for the treatment of both asthma and COPD. Although a Cochrane review was unable to show any major differences in outcomes between fluticasone/salmeterol and budesonide/formoterol for asthma (Lasserson *et al.*, 2011) other recent studies have found more favourable results for the treatment of COPD for budesonide/formoterol in terms of reduced number of exacerbations (Larsson *et al.*, 2013) and reduced pneumonia and pneumonia-related mortality (Halpin *et al.*, 2011; Janson *et al.*, 2013). These data in combination with market considerations may explain some of the trends found for budesonide/formoterol within the KY database.

The regression analysis suggested that men were more likely to be adherent and persistent with respiratory therapy despite the historical impression that women tend to be more cognisant with their health. Women have been suggested to face gender bias with regard to diagnosis and treatment of COPD that may explain this finding. Hypothetical care presentations to clinicians have shown that women are less likely

to receive a diagnosis of COPD than men even when clinicians are confronted with similar patient scenarios (Chapman *et al.*, 2001). Follow-up studies in real practice have suggested that women receive spirometry less often than their male counterparts (Watson *et al.*, 2004). There is a lack of similar research investigating gender bias in asthma but one study following patients in general practice with new nonspecific respiratory complaints (breathlessness, cough, sore throat, hyper-secretion) found that women remained less likely to be asked about their smoking habits, receive a pulmonary auscultation or be provided with a definitive diagnosis for their symptoms (Ruiz-Cantero *et al.*, 2007).

With COPD, differences between the sexes are the result of both historical and biological considerations. COPD was long considered a disease almost exclusively of men based on their predilection for tobacco use over women approximately 60 years ago leading to eventual and disproportionate development of the disease later in life. However, increasing use of tobacco among women occurred 20 years after men (Lopez *et al.*, 1994) and only recently have consequences such as COPD begun to emerge and be fully realised by clinicians. Additionally, as women have begun to develop COPD a number of differences in disease expression have also been discovered. Among men and women with COPD matched by their FEV_1, women were found to be younger with less smoking history and poorer scores in walking distance, quality of life and level of dyspnoea (de Torres *et al.*, 2005). Research has indicated that women may be more affected by COPD due to enhanced susceptibility to tobacco and a possible negative influence of sex hormones on airway function (Han, Postma*, et al.*, 2007).

How these differences in care between the sexes relate directly to adherence or persistence is not well evaluated, however women do appear to face additional barriers with regards to their use of medicines. Patients of all demographic categories are equally vulnerable to poor adherence (World Health Organization, 2003) but studies have suggested that women may be less adherent to therapy in some instances including antiretroviral therapy for human immunodeficiency virus (HIV) infection, preventive therapy after myocardial infarction and statin therapy for cardiovascular disease (Lauffenburger *et al.*, 2014; Lewey *et al.*, 2013; Puskas *et al.*, 2011). A recent claims analysis of 29.5 million patients in the USA for medication adherence across a variety of therapeutic classes found that while women were

more likely to use medication they were less likely to be adherent and to receive guideline-recommended treatment and monitoring (Manteuffel *et al.*, 2014). The results of the present study suggest that both asthma and COPD medicine use trends may mirror these previous trends.

Additionally, patients with COPD were found to have greater odds of adherence compared to patients with asthma. Due to the nature of the progressive decline in lung function in COPD these patients may experience more consistent and severe disease symptomology and may be inclined to be more adherent than patients with asthma. The inclusion of patients prescribed regular preventer therapy would assume that the population studied had chronic asthma; the natural episodic nature of patient symptoms in asthma may have resulted in sporadic treatment periods and treatment-free intervals resulting in a lower overall adherence. In these cases, patients may feel that therapy fails to provide any demonstrable benefit and the inconvenience of inhaled therapy may not be worth the health return on investment.

Among the inhaled therapies assessed in the regressions, LAMA therapy was associated with the best adherence/persistence among inhaled therapies which is likely to be a function of the increased convenience of once-daily dosing (Breekveldt-Postma *et al.*, 2007). Medication adherence is known to decrease as dosing frequency increases (Coleman *et al.*, 2012) and all other therapies in the present analysis have a standard twice-daily dosing regimen. Although efficacy for therapies in respiratory disease is largely determined by objective outcomes such as lung function, exacerbations and hospitalisations, the introduction of LAMA therapy was considered a ‘game changer’ with regard to improvement in patient-oriented outcomes such as health-related quality of life, exercise tolerance and dyspnoea (Decramer, 2006). These effects are more evident to a patient in the short-term and may encourage better adherence through positive reinforcement – a patient feels better after starting the medication and has incentive to continue taking it.

Theophylline was the only oral maintenance therapy assessed in the analysis and despite a relatively smaller number of patients treated overall, the preference for oral therapy was evident both for adherence and persistence – an effect that has been seen previously in children with asthma (Maspero *et al.*, 2001; Sherman *et al.*, 2001). Therapy with an ICS had the lowest percentage of patients with either

disease identified as having an adequate level of medication supply (MPR 80 to 120%) but was also found to have a comparatively high rate of adherence/persistence in the regression analyses. For adherence, this was likely to be influenced by the inclusion of oversupply in the binary outcome but for persistence the reasons are less clear. There may have been some influence of inhaler size on the results as most of the available combination therapy inhalers and LABAs are packaged in 60-dose or 120-dose units corresponding to a 30-day supply per inhaler. However, the most commonly utilised ICS (beclometasone and budesonide) are supplied in 200-dose units which correspond to as much as a 100-day supply for a single inhaler. This may have led to higher odds of persistence for ICS within our calculations as a single prescribing event provides a longer medication supply. An additional point to consider is the effect that ICS dose titration may have on adherence and persistence. It is possible that clinicians may initially prescribe a higher dose of ICS (or a higher number of doses from an inhaler) which is then scaled back based on the patient's symptoms. This may explain some variation in the results.

Medication persistence is not only a measure of long-term adherence but also of treatment stability as the TTD may be influenced by patients with therapy changes such as patients with asthma 'stepping up' from ICS therapy alone to combination inhaler therapy. The percentage of patients treated with more than one class of maintenance therapy was significantly higher among patients with COPD than with asthma and likely softened the effect of both COPD diagnosis and treatment with LAMA in the multivariable regression for persistence – both variables that were significant on a univariable basis and significant in the adherence regression. The shape of persistence curves and the further lessened persistence among patients with newly initiated therapy suggests that the overall low persistence is primarily influenced by the large drop-off of patients early in therapy often after the first two prescriptions. Interpretation of the regression data remains cautious; it is evident from the fit of the models that other explanatory factors relating to adherence and persistence were not included, such as device-related factors, patient preferences and other unknown contributions. This is a function of both the limitations in data availability with retrospectively collected data as well as the nature of adherence/persistence studies where modest model fits are relatively common because the problem is multifactorial.

5.4 Treatment investigations

5.4.1 Methods

Therapy classification

Patients with COPD who received prescriptions during 2008, in both the FV and KY databases, were isolated and their treatment was categorised into one of six pre-determined categories: (1) short-acting inhalers (SABA or SAMA) alone; (2) LABA only; (3) LAMA only; (4) combination therapy (ICS + LABA); (5) dual bronchodilator therapy (LABA + LAMA); or (6) triple therapy with ICS, LABA and LAMA (queries 33 – 44). Short-acting inhalers, OCS or theophylline were permitted as concurrent treatment for any therapy category with only exclusion of other maintenance therapies used to isolate patients. These groups were chosen based on what would be anticipated therapy recommended in NICE COPD guideline (National Institute for Health and Clinical Excellence, 2010). Patient and clinical characteristics were assessed according to therapy classification for both databases including age, sex, presence of co-morbid asthma and utilisation of SABA and OCS during 2008. FEV_1 % predicted was also assessed although only for the FV database as this information was unavailable in the KY database.

Licensed ICS prescribing

Prescribing of ICS for patients with COPD was further evaluated. Products containing an ICS (both single-agent inhalers and combination therapy inhalers) from 2007 – 2009 were queried (queries 45 – 46). Prescriptions were categorised by whether they were for a licensed dose and/or formulation for COPD. Only combination therapy inhalers in both the UK and the USA are licensed for the treatment of COPD albeit with different formulations and at different doses (Table 5.9).

Table 5.9: Licensed indications ICS-products for the treatment of COPD
Adapted from (Electronic Medicines Compendium, 2014a; Electronic Medicines Compendium, 2014c; Electronic Medicines Compendium, 2014d; GlaxoSmithKline)

Medication	UK license	USA license
Fluticasone/salmeterol	Seretide Accuhaler® 500/50: 1 puff twice daily	Advair Diskus® 250/50: 1 puff twice daily
Budesonide/formoterol	Symbicort® 400/12: 1 puff twice daily Symbicort® 200/6: 2 puffs twice daily	Symbicort® 160/4.5: 2 puffs twice daily

Recognising that a clinician may choose to utilise separate inhalers to administer combination therapy to a patient, single-agent ICS products were also assessed based on whether they were prescribed at licensed COPD doses. Although unlicensed for COPD, fluticasone and budesonide were included in this analysis as component parts of their corresponding combination therapy inhalers; beclometasone (generic beclometasone and Clenil Modulite® in the FV database, and Qvar® in the KY database) was also included since it was a widely utilised therapy. Single-agent ICS doses were categorised in the same manner as their root combination therapy inhaler; generic beclometasone/Clenil Modulite® considered equipotent to budesonide and Qvar® was considered twice as potent as budesonide as in previous analyses. A correction was also applied to accommodate formulation differences in budesonide-containing products; doses in the KY database were multiplied by a factor of 1.25 to align with the FV database (based on differences in ex-valve and ex-actuator doses). Single-agent ICS products were cross-referenced with prescriptions for single-agent LABA products to determine whether a patient was indeed being prescribed combination therapy. This was achieved by using the date of the ICS prescription as marker and searching for single agent LABA prescriptions within 100 days (before or after) the ICS prescription date of issue (queries 47 – 48). Figures were reported for three-year cumulative totals but investigated on a yearly basis to assess for any trends.

In addition to categorisation the mean dose of combination therapy products and single-agent ICS products were compared between the FV and KY databases. Estimates were made for combination therapy and single-agent ICS separately. A sensitivity analysis excluding patients with co-morbid asthma was also conducted for

the licensed combination therapy inhalers to quantify any influence. Mean doses were compared using 2-sample t tests.

Predictors of spirometry

An analysis was conducted to determine predictors of spirometry in the FV database (query 49). Patients with COPD who received treatment between January 2009 – December 2009 were determined. From this, two groups were isolated: patients with first recorded spirometric testing within 12 months prior or 6 months after their first prescription in 2009 and patients with no record of any spirometric testing. The inclusion time frame was made as to create a cohort of patients receiving active treatment stratified by whether they had been assessed by spirometry. Patients with recorded spirometry more than 12 months prior were excluded to best determine predictors for first recorded spirometry in the database. Although data collection for the FV database was only active for 2007 – 2009, historical data on spirometry was available for patients based on what was recorded in the medical record and then transferred into the FV database. The date of spirometry, or the date of first prescription in the inclusion period if no spirometry was performed, was considered the index date. Demographic characteristics (age and sex) and clinical characteristics (smoking status, asthma co-morbidity and characterisation of newly diagnosed COPD) were quantified. Prescriptions for short-acting inhalers (SABA or SAMA) and OCS in the 12 months previous to the index date were quantified as surrogate markers for symptom control and exacerbations, respectively. Smoking status was assessed using the most recent data entry before the index date. The patient was considered to have 'newly diagnosed' COPD if the diagnosis date was within 12 months prior or 6 months after the index date.

Patient characteristics were stratified according to spirometric testing (yes/no), and compared using Mann-Whitney tests for continuous variables, and binomial proportion confidence intervals and chi-squared tests for categorical data. A step-wise forward binary logistic regression model was utilised to determine predictors of spirometric testing. Variables were assessed on a univariable basis with significant variables filtered into the final multivariable model, with α set at 0.05 for entry and 0.10 for removal. Results were reported with odds ratios and 95% confidence intervals; model fit was assessed using the c-statistic. The effect of missing data was handled using three methods: (1) treating missing data categorically; (2)

analysing only complete cases; and (3) utilising multiple imputation to complete missing data. Significance of each variable was compared across three methods to assess overall robustness of the results.

5.4.2 Results

5.4.2.1 Therapy classification

A total of 3,764 patients in the FV database were classified into the pre-specified treatment categories: 80.9% of those who received any treatment during 2008. A further 1,048 patients in the KY database were similarly assessed: 42.8% of all patients who received any treatment during the year. The most common option in the FV database was triple therapy (44.6%) followed by combination therapy in 22.6% of patients (Figure 5.20). Triple therapy was significantly less utilised in the KY database (11.1%) with short-acting inhaled therapy the most common choice in 45.4% of patients. Single-agent LABA therapy was used infrequently (1.3% and 1.2%) as was double bronchodilator therapy (1.7% and 0.7%) in the FV and KY databases, respectively.

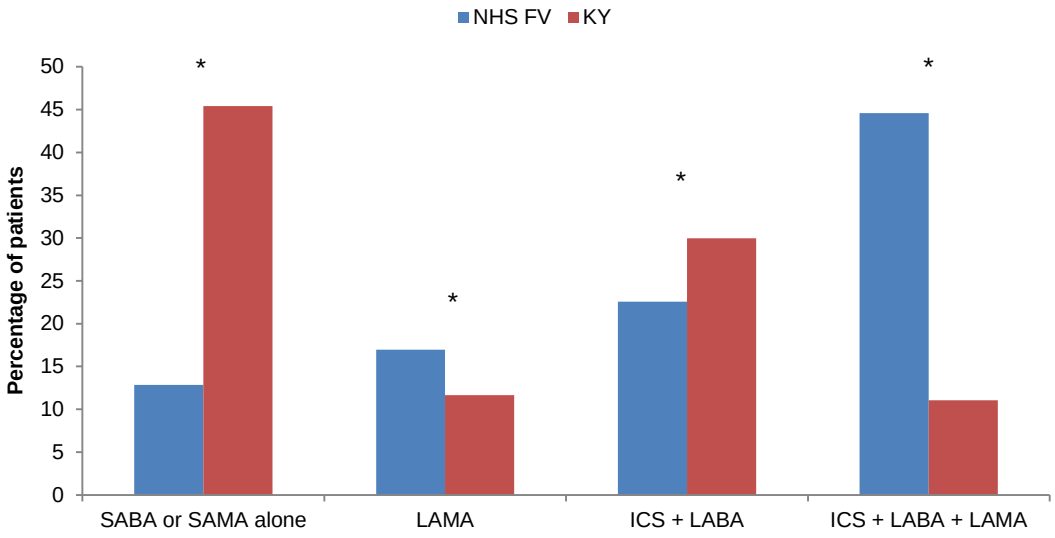


Figure 5.20: Comparison of COPD therapy categorisation in the FV and KY databases (2008)
** p<0.05 for comparison between databases*

Outside these pre-specified groups the most commonly utilised therapies in the FV database were ICS alone (7.9%), ICS + LAMA (5.3%) and OCS/antibiotics alone (5.7%). The majority of patients in the KY database received alternative therapies

the most common overwhelmingly being OCS/antibiotics alone (53.1%) followed by ICS alone (4.0%) and ICS + LAMA (0.9%).

Patients who received LAMA-containing therapies were slightly older than other patients particularly in the KY database (Table 5.10 (a) and (b)). No particular pattern was noticed for sex with the exception of women receiving LAMA alone in the KY database. Asthma co-morbidity was highest among patients receiving combination therapy at 27.7% in the FV database and 63.7% in the KY database. In the FV database median FEV_1 % predicted decreased as the therapy progressed from as-needed therapy through single, double and triple maintenance therapy (Table 5.10(b)). The number of doses/day of SABA or SAMA and courses of OCS in the KY database also increased as therapy progressed: this trend was not as clear for the FV database but was marginally apparent with the exception of those on no maintenance therapy, who received the highest daily dose of SABA/SAMA. The use of OCS was more commonly among patients receiving ICS-containing therapies.

Table 5.10a: Patient/clinical characteristics within COPD therapy classification (2008) in the FV database

Characteristic	Total	Therapy			
		SABA or SAMA alone	LAMA alone	ICS + LABA	ICS + LABA + LAMA
Female, n (%)	1,944 (51.6)	258 (53.5)	322 (50.4)	451 (53.1)	857 (51.0)
Median age (IQR)	69 (62-76)	68 (60-76)	70 (62-76)	69 (61-76)	70 (62-77)
Asthma, n (%)	696 (18.5)	53 (11.0)	50 (7.8)	235 (27.7)	348 (20.7)
FEV_1, n (%)	2,873 (76.3)	305 (63.0)	480 (75.1)	606 (71.4)	1,386 (82.5)
Median FEV_1 % predicted (IQR)	61 (48-74)	68 (58-77)	65 (55-77)	62 (48-77)	57 (44-70)
SABA or SAMA, n (%)	3,434 (91.2)	484 (100.0)	498 (77.9)	764 (90.0)	1,588 (94.6)
Doses per day, median (IQR)	4.3 (2.0-8.1)	4.9 (2.5-8.6)	3.2 (1.3-6.4)	4.6 (1.9-8.0)	4.6 (2.2-8.5)
OCS, n (%)	1,140 (30.3)	50 (10.3)	90 (14.1)	275 (32.4)	704 (41.9)
Courses, mean (SEM)	3.4 (0.11)	3.0 (0.56)	2.9 (0.45)	3.4 (0.20)	3.5 (0.14)

Table 5.10b: Patient/clinical characteristics within COPD therapy classification (2008) in the KY database

Characteristic	Total	Therapy			
		SABA or SAMA alone	LAMA alone	ICS + LABA	ICS + LABA + LAMA
Female, n (%)	544 (51.9)	247 (51.9)	69 (56.6)	159 (50.6)	55 (47.4)
Median age (IQR)	56 (48-63)	54 (46-61)	59 (52-65)	55 (48-64)	58 (52-66)
Asthma, n (%)	490 (46.8)	197 (41.4)	28 (23.0)	200 (63.7)	58 (50.0)
SABA or SAMA, n (%)	807 (77.0)	476 (100.0)	60 (49.2)	168 (53.5)	87 (75.0)
Doses per day, median (IQR)	2.2 (1.1-4.9)	1.9 (0.9-4.3)	2.3 (1.2-5.1)	2.5 (1.3-4.8)	3.3 (1.7-5.9)
OCS, n (%)	314 (30.0)	132 (27.7)	18 (14.8)	102 (32.5)	54 (46.6)
Courses, mean (SEM)	2.3 (0.14)	1.9 (0.16)	1.9 (0.40)	2.5 (0.26)	3.2 (0.46)

5.4.2.2 Licensed ICS prescribing

In the FV database 65.6% of prescriptions for fluticasone/salmeterol and 69.6% of prescriptions for budesonide/salmeterol were for licensed doses of 1,000 micrograms daily and 800 micrograms daily, respectively ($p<0.001$) (Figure 5.21). All the prescriptions for licensed dose budesonide/salmeterol were for the approved formulations while over half of licensed dose fluticasone/salmeterol prescriptions were for formulations other than the 500/50 microgram strength of Seretide Accuhaler®. Almost one-third of prescriptions for fluticasone/salmeterol were at doses lower than approved with the large majority at the USA-licensed dose of 500 micrograms daily: half the UK licensed dose. The number of prescriptions for both appropriate dose and formulation increased step-wise from 2007 – 2009, from 15.5 to 37.5% for fluticasone/salmeterol and 67.1 to 73.7% for budesonide/salmeterol. Among single-agent ICS products rates of licensed dose prescribing were lower at 57.0% for fluticasone (total prescription count = 5,132), 45.8% for budesonide (n=1,857) and 27.0% for beclometasone (n=7,556). The rates of licensed dose prescribing remained relatively stable across the three years. A total of 1,498 (29.2%) prescriptions for single-agent fluticasone also had concurrent prescribing of a separate LABA. This was lower among budesonide (346; 18.6%) and beclometasone/Clenil Modulite® (1,658; 21.9%). A total of 3.5% of all assessed prescriptions had unclear dosing instructions and were unable to be evaluated.

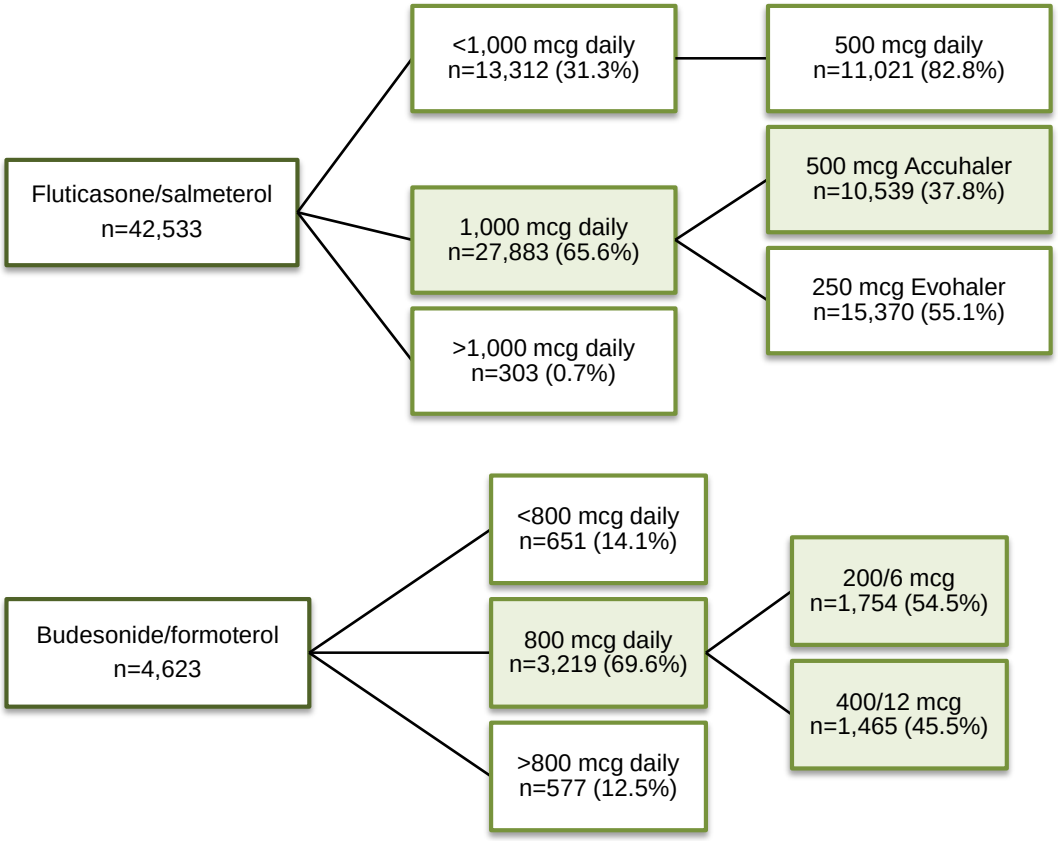


Figure 5.21: Breakdown of ICS prescribing for patients with COPD in the FV database (2007 – 2009)
Green shaded boxes indicate licensed dose and formulations

In the KY database, licensed dosing was more frequent among prescriptions for budesonide/formoterol compared to fluticasone/salmeterol (80.8 vs. 64.7%, p<0.001) (Figure 5.22). For both combination therapy inhalers all prescriptions under licensed dosing were for the indicated formulation and rates of licensed dose and formulation prescribing showed no clear trend across the three years assessed. A total of 21.2% of prescriptions for fluticasone/salmeterol were dosed at higher than licensed doses almost uniformly at the UK-licensed dose of 1,000 micrograms daily. The rate of licensed dosing among single-agent ICS products was similar at 55.7% for fluticasone (n=420), 60.1% for budesonide (n=148) and 63.8% for Qvar® (n=185). Figures for each individual year again showed no temporal trend. Budesonide had the highest rate of concurrent LABA prescribing (46; 31.1%) followed by fluticasone (53; 12.6%) and Qvar® (22; 11.9%).

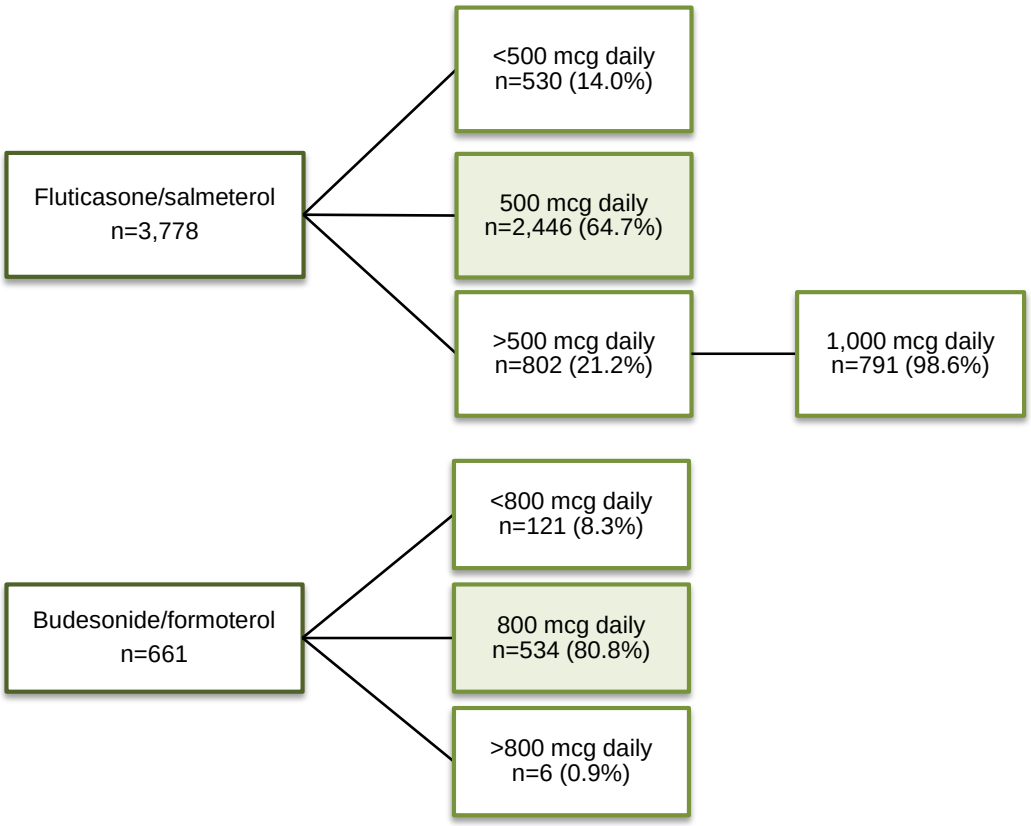


Figure 5.22: Breakdown of ICS prescribing for patients with COPD in the KY database (2007 – 2009)
Green shaded boxes indicate licensed dose and formulations

The mean dose of fluticasone/salmeterol was 832 micrograms daily and 568 micrograms daily in the FV and KY databases, respectively ($p<0.001$); the mean dose for budesonide/salmeterol products was higher in the FV database at 834 micrograms daily compared to 729 micrograms daily in the KY database ($p<0.001$). Doses of fluticasone/salmeterol prescriptions issued to the pure cohort of patients with COPD and no co-morbid asthma were similar to the full cohort in the FV database (833 vs. 832 micrograms, $p=0.796$) but slightly lower in the KY database (545 vs. 568 micrograms, $p=0.001$). Among prescriptions for budesonide/formoterol, the opposite was true with doses were lower in the FV database (806 vs. 838 micrograms, $p<0.001$) and similar in the KY database (720 vs. 729 micrograms daily, $p=0.530$).

Mean doses for single-agent fluticasone and budesonide were lower than their corresponding combination therapy inhalers in the FV database at 804 micrograms daily for fluticasone and 776 micrograms daily for budesonide. The mean dose of

beclometasone/Clenil Modulite® was the lowest overall at 652 micrograms daily. In the KY database, mean doses for single-agent products were higher than combination therapy inhalers at 583 micrograms daily for fluticasone and 880 micrograms daily for budesonide. The mean dose of Qvar® (in beclometasone-equivalent) was 720 micrograms daily.

5.4.2.3 Predictors of spirometry

A total of 1,992 patients met inclusion criteria for the analysis representing 1,589 patients (79.8%) with a recorded history of first spirometry during the inclusion period (Table 5.11). A total of 2,619 further patients who received therapy during this period had historical spirometry records more than a year prior; of the total 4,611 patients treated in 2009, 4,208 patients (91.3%) had a history of spirometry. Among those assessed patients who received spirometry were predominantly male with either current or previous tobacco use. More patients with spirometry had been diagnosed with their COPD within the previous year while more patients without spirometry had been given a co-morbid diagnosis of asthma. The use of SABA or SAMA inhalers as well as OCS was similar between groups both as a function of the number of patients receiving these therapies and the number of canisters/courses received. Data were missing for smoking status to a larger extent in patients who received spirometry.

Table 5.11: Patient characteristics stratified by spirometric testing in the FV database (2009)

Characteristics, n (%) (unless noted otherwise)	With spirometry (n=1,589)	Without spirometry (n=403)	p-value for difference
Male	787 (49.5)	167 (41.4)	<0.001
Median age, years (IQR)	69 (60-75)	72 (60-81)	<0.001
< 40	8 (0.5)	20 (5.0)	<0.001
40-49	91 (5.7)	22 (5.4)	
50-59	253 (15.9)	56 (13.9)	
60-69	501 (31.5)	84 (20.8)	
70-79	547 (34.4)	98 (24.3)	
≥ 80	189 (11.9)	123 (30.5)	
Smoking status			
Never smoker	93 (5.9)	77 (19.1)	<0.001
Current smoker	544 (34.2)	147 (36.5)	
Former smoker	589 (37.1)	171 (42.4)	
Missing data	363 (22.8)	8 (2.0)	
Comorbid asthma	271 (17.1)	97 (24.1)	0.016
Newly diagnosed COPD	674 (42.4)	107 (26.6)	<0.001
Use of OCS in previous 12 months	624 (39.3)	157 (39.0)	0.954
Number of courses, median (IQR)	2 (1-5)	1 (1-6)	0.672
Use of SABA or SAMA in previous 12 months	1,515 (95.3)	392 (97.2)	0.098
Number of canisters, median (IQR)	8 (3-16)	8 (3-17)	0.164

In the regression analysis female sex and a co-morbid asthma diagnosis were associated with decreased odds of spirometric testing (Table 5.12). Additionally, terminal age categories (less than 40 years old or greater than or equal to 80 years old) led to reduced odds of receiving spirometry. The use of tobacco (whether current or previous) and newly diagnosed COPD increased the odds of receiving spirometry. Use of OCS in the year prior did not meet significance on a univariable basis but each additional canister of SABA prescribed during the 12 months prior to the index date was associated with a 2% increase in the odds of receiving spirometry. The fit of the model as assessed by the c-statistic was fair (0.75).

Table 5.12: Multivariable logistic regression for spirometry utilisation in the FV database (2009)
† *univariable analysis with spirometry utilised as outcome*
‡ *multivariable analysis adjusted by sex, age, smoking status, co-morbid asthma, timing of COPD diagnosis, and use of SABA in previous year, with spirometry utilised as outcome*
§ *model fit assessed by c-statistic: 0.75 (95% CI: 0.72-0.78)*

Variable	Crude OR (95% CI) †	Adjusted OR (95% CI) ‡§	Adjusted OR p-value
Sex			
Male	1 (reference)	1 (reference)	0.012
Female	0.72 (0.58 – 0.90)	0.73 (0.58 – 0.93)	
Age (years)			
< 40	0.10 (0.04 – 0.25)	0.07 (0.02 – 0.21)	<0.001
40-49	1 (reference)	1 (reference)	
50-59	1.10 (0.63 – 1.89)	1.16 (0.65 – 2.07)	
60-69	1.44 (0.86 – 2.43)	1.68 (0.96 – 2.93)	
70-79	1.35 (0.81 – 2.25)	1.63 (0.93 – 2.86)	
≥ 80	0.37 (0.22 – 0.62)	0.51 (0.28 – 0.91)	
Smoking status			
Never smoker	1 (reference)	1 (reference)	<0.001
Current smoker	3.06 (2.15 – 4.36)	2.18 (1.46 – 3.24)	
Former smoker	2.85 (2.02 – 4.03)	2.15 (1.48 – 3.14)	
Co-morbid asthma	0.65 (0.50 – 0.84)	0.69 (0.51 – 0.94)	0.018
COPD diagnosis			
Pre-existing	1 (reference)	1 (reference)	<0.001
In previous year	2.04 (1.60 – 2.60)	1.74 (1.33 – 2.28)	
SABA (canisters)	1.02 (1.01 – 1.03)	1.02 (1.01 – 1.04)	0.001

CI: confidence interval; COPD: chronic obstructive pulmonary disease; OR: odds ratio; SABA: short-acting beta agonist

Due to missing data for smoking status in 18.6% of total patients complete case and multiple imputation scenarios were performed to verify the results. Results remained robust with adjusted OR for current and former smokers at 2.16 (95% CI: 1.45-3.21) and 2.15 (95% CI: 1.47-3.14) for complete cases and 2.15 (95% CI: 1.82-2.55) and 2.08 (95% CI: 1.77-2.44), respectively. All other variables remained stable as well.

5.4.3 Discussion

Treatment recommendations for COPD are based on a number of individual patient considerations (such as FEV_1 % predicted and history/risk of exacerbations) as opposed to the more generalised and linear step-wise approach that covers most treatment of patients with asthma. However, there is some degree of progression through various treatments from short-acting inhalers for intermittent relief (for patients with mild disease) to triple maintenance inhalation therapy (for the most severe patients). Analysis of patients' treatment found the most common therapy options in either database were at opposite ends of the spectrum with the majority of patients in the FV database receiving triple therapy and the majority of patients in the KY database receiving SABA or SAMA therapy only.

Patient and clinical characteristics for each main type of COPD therapy were assessed for differences similar to step therapy for asthma. Median FEV_1 % predicted was lower among patients receiving ICS-containing therapies as would be anticipated based on the current recommendations for this therapy. However, both the medians (62% for combination therapy and 57% for triple therapy) indicate use of these therapies among patients with relatively sustained lung function contrary to some recommendations. The UK licensing for Seretide® allows use in patients with an FEV_1 % predicted less than 60% (in addition to a history of repeated exacerbations and significant symptoms despite regular bronchodilator therapy) but the SMC recommendations are more stringent with an FEV_1 % predicted threshold of less than 50%. In 2008, GlaxoSmithKline submitted an application to the SMC to widen the approved use of Seretide® to this lower threshold. This application was unsuccessful based on a lack of demonstrated economic case for patients within an FEV_1 % predicted range of 50 to 59%, especially when the null effect on mortality for the therapy was coupled with an increased risk of pneumonia (Scottish Medicines Consortium, 2008). Both licensing and SMC recommendations for Symbicort® indicate an FEV_1 % predicted threshold of less than 50% (Scottish Medicines Consortium, 2004). Based on the median and IQR of all spirometry values in the FV database (from the demographic analysis), less than a quarter of patients would meet criteria for treatment with any ICS-containing therapy based on spirometric classification alone.

In the revised GOLD classification of overall COPD severity exacerbation risk can substitute for airflow limitation in determining the best course of therapy. The use of OCS (both the proportion of patients receiving and the number of courses received) was higher in these therapy groups suggesting concordance with guideline recommendations. However, this demonstrates an area where the most updated international clinical guidance (GOLD) differs from older guidance (NICE), and where clinicians may choose to follow different product guidelines (either from the official licensing or SMC recommendations). Although SMC recommendations are not designed to be regulatory their advice is widely utilised by health boards in NHS Scotland for designing local formularies and is paramount in forward service planning within a constrained publicly-funded healthcare budget. For instance, local prescribing guidance in NHS Forth Valley for Seretide® uses the SMC-recommended 50% threshold (NHS Forth Valley, 2012), however, the results of this analysis suggest that prescribers may not be following this recommendation stringently.

Appropriateness of therapy is difficult to ascertain with this type of data although some suggestions may be present. For instance, in the FV database, the highest dose/day of SABA or SAMA was seen in the group receiving only this therapy and no maintenance inhalers. This may indicate a need for therapy advancement in this group even though they only accounted for 12.9% of the patients assessed. Conversely, the same group in the KY database constituted 45.2% of the patients assessed and yet had the lowest dose/day of SABA or SAMA. It is possible that patients in the KY database had milder disease overall particularly with the younger age of the COPD population as shown in the demographics analysis – although unfortunately spirometry data to substantiate this was not available.

It is evident that the rate of concurrent asthma is high in the KY database and that this was particularly the case for patients treated with combination therapy for COPD. The likelihood of diagnostic mis-coding continues to be the main concern made even more probable with the higher rate of co-morbidity in patients not receiving LAMA-containing therapies (which would only be used for COPD). Three scenarios are possible: (1) patients truly have one disease, and have inadvertently also been mis-coded with the other, (2) patients have either mixed or undetermined lung disease and are purposely coded with both diseases or (3) patients have

neither chronic disease but other respiratory illnesses that are being coded (purposely or not) incorrectly. Unfortunately, the KY database lacks other indicators to help investigate the likelihood of the scenarios; for instance, data on smoking status or spirometry would be valuable to this effect.

At the time of data collection for these studies only two combination therapy inhalers were licensed for use in COPD: fluticasone propionate/salmeterol (approved in the UK [2002] and USA [2003]) and budesonide/formoterol (UK [2003]; USA [2009]). A third product, beclometasone/formoterol was also available (Fostair®, UK [2007]) but is licensed only for asthma. Since this time period several other combination therapy products have come to market including mometasone/formoterol (Dulera®, USA [2010]) and fluticasone furoate/vilanterol (Breo Ellipta®, USA [2013]; Relvar Ellipta®, UK [2013]). Currently, mometasone/formoterol is only indicated for the treatment of asthma while fluticasone furoate/vilanterol is indicated for COPD in the USA but for both asthma and COPD in the UK. Umeclidinium bromide/vilanterol (Anoro Ellipta®, USA [2013]) is a dual bronchodilator that has been approved for COPD in the USA with filing pending in the UK; it consists of a new LAMA and LABA and is dosed on a once-daily basis. Clinicians may regard specific licensing for asthma or COPD to be a regulatory hurdle and believe the effects from a particular ICS or LABA to be class-wide and not specific to pharmacologic agent. Use of alternative combination therapies for COPD may have started before they gained approval if the therapy was already on the market and widely utilised for the treatment of asthma as in the case of budesonide/formoterol in the USA.

Unlike asthma, however, ICS for the treatment of COPD are only licensed with concurrent LABA therapy. While medicines are commonly utilised off-label for a variety of reasons, licensed indications for ICS products in COPD are based on a specific evidence base. The TRISTAN and TORCH studies provided support for combination therapy over an ICS or LABA alone for improvements in lung function, less symptoms and lower rates of exacerbations (Calverley, Pauwels*, et al.*, 2003; Calverley *et al.*, 2007). Two subsequent Cochrane reviews have reviewed the comparisons of combination therapy over ICS and LABA for COPD. Compared to ICS alone the use of combination therapy among 15 studies and over 7,000 patients resulted in lower rates of exacerbations (RR: 0.87, 95% CI: 0.80-0.94) mortality (OR: 0.78, 95% CI: 0.64-0.94) and improved results for lung function and quality of life

(Nannini *et al.*, 2013). Fourteen studies and nearly 12,000 patients were included in the comparison against LABA alone: the review found that exacerbation rates were decreased among those receiving combination therapy (RR: 0.76, 95% CI: 0.68-0.84), however, these results were contaminated by issues with statistical heterogeneity and bias in included studies (Nannini *et al.*, 2012). Improvements in quality of life, symptoms and lung function were also noted for combination therapy although the clinical significance of these improvements is debated (Nannini *et al.*, 2012). These statements are also supported in guidance provided by the MHRA with a specific reminder that ICS should not be used alone in COPD (Medicines and Healthcare products Regulatory Agency, 2009). However, 70 to 80% of prescriptions in the FV database and 80 to 90% of prescriptions for ICS in the KY database failed to demonstrate concurrent LABA therapy.

Additionally, unlike asthma, a dose-response curve has not been ascertained for COPD and the ICS component of combination therapy is currently only indicated at fixed high doses. However, these high doses are specific to each medication and what has been studied in clinical trials as the indicated dose of budesonide is 800 micrograms daily, while the indicated dose of fluticasone ranges from 500 to 1,000 micrograms daily (equivalent to 1,000 to 2,000 micrograms of budesonide daily). Analysis of mean ICS doses showed that some patients were being under-dosed, particularly among those receiving beclometasone-containing products. It is not known whether lower doses are effective in the management of patients with COPD and therefore represent a significant area for optimisation in both Kentucky and NHS Forth Valley.

It is important to note that the licensed dosing in the UK and USA even within the same medication (fluticasone/salmeterol) is two-fold different at 1,000 micrograms daily and 500 micrograms daily for the fluticasone component, respectively. Mean doses in either database reflected this anticipated difference, although on average, patients in the FV database were receiving more sub-therapeutic doses (based on UK product labelling). The original FDA approval of Advair® for COPD noted that while study data showed the combination product to be superior to each of its component parts for FEV_1 improvement there was a lack of evidence showing superiority of the 1,000 microgram daily regimen over the 500 microgram daily regimen (GlaxoSmithKline). As the higher dose would increase systemic exposure

to fluticasone and increase the potential for adverse effects, only the lower dosing regimen was granted approval. However, with disagreement in international labelling for the same medication it is feasible that either dose may be deemed by clinicians to be appropriate.

Prescriptions were evaluated in two ways: those that met licensed dosing and those that met both licensed dosing and licensed formulation. The analysis was performed this way as the availability of various ICS products would make alternate scenarios possible. For instance, a patient with COPD might prefer or require pMDI therapy rather than DPI therapy and may be prescribed Seretide Evohaler® 250 micrograms 2 puffs twice daily (the licensed dose and alternative formulation) as opposed to Seretide Accuhaler® 500 micrograms 1 puff twice daily (the licensed dose and formulation). The NHS Forth Valley formulary and NHS Forth Valley COPD guidelines mention this scenario but with the plain warning that only the Accuhaler® formulation is licensed and the Evohaler® formulation is significantly more expensive to deliver the same treatment (Forth Valley Area Drug and Therapeutics Committee, 2012; O'Hara, 2012). It is also plausible that a patient may receive fluticasone and salmeterol in separate inhalers although the reasons for this are not well justified and a single inhaler is overwhelmingly preferred to help maintain adherence with both components. However, as shown in this analysis this is often not the case, whether purposely or inadvertently, and often the LABA component is not prescribed. It should also be mentioned that formulary restrictions from third-party insurance in the USA may exact limitations on doses/formulations of inhalers are used for a particular patient, which may account for some of the results.

Among published prevalence estimates COPD has been described by several methods including patient symptoms, physician diagnosis, spirometric testing and disease modelling. All international treatment guidelines agree that spirometry remains the gold standard tool for the diagnosis and management of COPD and can be easily utilised in general practice although actual uptake and use has been reported to be low commonly at one-third of patients or less in the USA and other areas of the world (Buffels *et al.*, 2009; Joo, Lee and Weiss, 2008; Volkova *et al.*, 2009; Weidinger *et al.*, 2009). The accuracy of other measures to diagnose COPD compared to spirometry has been poor making this issue even more pertinent (Abramson *et al.*, 2012; Schneider *et al.*, 2009). The rate of spirometry utilisation to

support diagnosis and monitoring in the UK has little published data; however, one would anticipate a different scenario based on the influence of the QOF scheme and its provision of incentive for the use of spirometry. Current threshold standards ask practices to obtain diagnostic confirmation using post-bronchodilator spirometry in at least 40% of patients with COPD, and record of FEV_1 in the last 15 months in at least 40% of these patients, with more incentive provided for better achievement levels (Information Services Division Scotland, 2014). Despite its voluntary nature, this scheme has likely underpinned high utilisation of spirometry in UK general practice as attainment of these parameters for NHS Scotland as a whole in 2011/2012 was estimated at 96.1% and 98.7%, respectively (Information Services Division Scotland, 2014). Directly comparable data prior to the introduction of the QOF is sparse but one historical analysis from Wales estimated that spirometric confirmation of COPD diagnosis across approximately 200 GP practices was widely variable but only reached a median of 37% (Bolton *et al.*, 2005).

A total of 91.3% of patients treated in 2009 had a record of spirometry at some point and 79.8% had received spirometry within an 18-month window of their first prescribing during the year. Current recommendations, both through clinical guidelines and via the QOF, recommend spirometry both as a diagnostic tool and a mechanism to follow and track disease progression. It is worthwhile to note that the analysis included patients with their first recorded spirometry in the database, regardless of whether they were newly or previously diagnosed with COPD. This may have resulted in a higher reported rate of spirometry than other studies since the opportunity for spirometry should increase with patients who have had a diagnosis for a longer period of time. However, it was evident from the regression that spirometry was being performed more often for new diagnoses and less often among patients with establishes diagnoses. The window for assessing spirometry in this analysis was set at 18 months which should have captured all patients meeting QOF testing standards which is recommended every 15 months. It is possible that patients without a record of spirometry in may have received it but not had it recorded within the GP medical record and therefore outside of the capture of the FV database. This may have occurred during secondary care admissions for COPD exacerbations. However, in these cases recording of spirometry ideally would have still occurred, either to fulfil reporting continuity and QOF requirements from hospital

admission, or with a follow-up spirometric assessment to re-assess the patient after recovery from the exacerbation but still may not have been recorded.

Many factors can affect whether a patient receives spirometry. From the clinician perspective identifying which patients should receive spirometry to evaluate or follow-up their symptoms is paramount. A lack of systematic approach on how to evaluate a breathless patient has been suggested among trainee doctors which creates a barrier to spirometry use (Roberts *et al.*, 2011). Other reasons include lack of understanding of guideline recommendations, poor access and/or understanding of how to perform spirometry accurately or belief that the test will be unlikely to change a patient's treatment course (Joo *et al.*, 2009). On the patient side, a study in the USA looking at determinants of testing found age, dyspnoea on exertion and cough to positively correlate with receiving spirometric testing (Joo *et al.*, 2011). Although the retrospective data in this analysis limited the ability to evaluate such factors an increasing use of SABA in the year prior to spirometry was found to be a positive predictor and was included to serve as a surrogate for degree of breathlessness. The variability of spirometry use among certain patient groups is important because it may influence the pharmacological treatment and ultimately the quality of care patients with COPD receive. One analysis among newly-diagnosed patients with COPD treated at Veterans Affairs (VA) facilities in the USA found that after receiving spirometric testing, patients were prescribed comparatively greater quantities of medication including ICS, LABA and ipratropium compared to before their testing (Joo, Lee, Au*, et al.*, 2008).

The odds of receiving spirometry in the present analysis were concentrated at 40 to 79 years old, which is reasonably anticipated based on the peak incidence and prevalence for the disease found in population-based studies (van Durme *et al.*, 2009). Although the lack of spirometric testing in patients less than 40 years old might be expected the similar lack of testing among patients 80 years and older is noteworthy. Another USA study discovered similar results among patients older than 75 years (Han, Kim*, et al.*, 2007). Consultation rates in general practice for COPD in Scotland increase steadily with age, with 242.1 consultations per 1,000 patient population among men aged 75 years and older (Practice Team Initiative, 2013b). This suggests that patients of most advanced age are consulting their GPs for their COPD but are not undergoing spirometric testing. These patients, as a function of

their age and disease state may be unable to complete testing due to poor ventilatory capacity or may opt out of testing for other reasons that this analysis is unable to discern. More worrying, however, is the possibility that it may also relate to GPs and their motivation to recommend spirometric testing for this patient group based on 'ageism' or hesitancy to pursue aggressive diagnostic work-ups in older patients. Sex was also found to be a discriminating predictor for performing spirometry. As discussed previously, women have been found to have a higher genetic susceptibility to COPD as well as a greater degree of symptoms than their male counterparts for the same level of lung function. This analysis and others have confirmed the gender bias women face in regards to spirometry use (Laitinen *et al.*, 2009; Watson *et al.*, 2004). Despite the historical perspective of COPD as a disease of men, smoking and COPD death rates in women have rapidly approached those of men in recent years (Thun *et al.*, 2013), making addressing gender disparities within COPD even more important.

With this information in mind regarding which patients are receiving spirometric testing in general practice the next logical question is the diagnostic accuracy of diagnoses within the FV database. The database was collected as a function of patients listed on practice disease registers and therefore has been assessed as a population of 'physician-diagnosed' asthma or COPD. Several studies have evaluated the accuracy of such registers. One study among GP practices in Devon found that of 580 patients listed on COPD registers spirometric confirmation of diagnosis was only found in 422 (72.8%) patients (Jones *et al.*, 2008); further studies in Australia estimated this figure at 57.8% and 65% (Abramson *et al.*, 2012; Zwar *et al.*, 2011). A systematic review of 24 studies evaluating the quality of various diagnostic registers in general practice found significant heterogeneity with mixed findings of correctness and completeness across several disease states (Jordan *et al.*, 2004). Data from the FV database demographic analysis found that only 75.2% of patients with recorded full spirometry data met FEV_1/FVC diagnostic criteria in line with rates from these previous studies. However, it should be noted that the previous studies prospectively ascertained spirometry as a part of the study protocol while in the FV database these data were obtained retrospectively. It is possible that these data has been incorrectly recorded (resulting in an artificially higher rate of accuracy), inadvertently omitted (resulting in a lower rate of accuracy) or a combination of both scenarios. Despite the known problems with diagnostic

registries it is important to note that patients included in this body of work were those receiving active therapy during 2007 – 2009. While it is difficult to diagnostically verify this retrospective cohort they do represent the 'real world' patients being treated for respiratory disease (whether correctly or incorrectly) and therefore remain important in their own right.

5.5 Conclusion

The demographics of patients with COPD in Kentucky are notably different than those of patients in NHS Forth Valley due to the database structure and possibly a greater influence of tobacco use and occupational exposures. Patients with COPD were found to have similar patterns to those with asthma with regards to medication adherence and persistence although comparatively a diagnosis of COPD alone seems to result in improved medicine use behaviours compared to asthma. The use of un-licensed ICS doses and formulations for the treatment of COPD was common despite a lacking evidence base. The use of spirometry in NHS Forth Valley was high among comparable estimates, but was suggestive of particular disparities which require further evaluation.

Chapter 6:

Conclusion

6.1 Summary of key clinical findings

This programme of research has resulted in a number of findings that build upon existing literature and help to identify areas for continuing quality improvement (Figure 6.1); specific clinical areas and their corresponding expanded discussions in the text are noted here. Adherence and persistence was found to be low in both diseases and would benefit from a focus on identifying and assisting barriers to optimal medicine use behaviour with inhaled therapies (sections 4.3.2.4, 4.3.2.5, 5.3.2.3, 5.3.2.4). The prescribing of ICS for both asthma (widespread utilisation of high-dose therapy; section 4.3.2.3) and COPD (widespread utilisation of un-licensed doses; section 5.4.2.2) is a significant area for development, particularly surrounding the education and understanding of ICS potencies across available products among clinicians, as evidenced by the results of the survey questionnaire (section 4.4.2.3). For asthma, the widespread utilisation of high-dose combination therapy in NHS Forth Valley (sections 4.4.2.1 and 4.4.2.2) requires justification for clinical appropriateness which could not be verified in this work but should be further investigated to prevent unintentional escalation of dosing. Additionally, the choice of therapy at step 3 of the BTS/SIGN asthma guideline requires further evaluation of the literature ensure guideline recommendations are clear and that patients receive optimal therapy (section 4.4.2.1). For COPD, there appears to be a significant number of patients listed on practice disease registers, but with spirometry values failing to diagnostically verify the disease (section 5.2.2.4). The use of spirometry was found to be high among practices in NHS Forth Valley compared to previous published estimates but there appear to be disparities in the patients who receive the testing that could be further investigated and addressed (section 5.4.2.3).

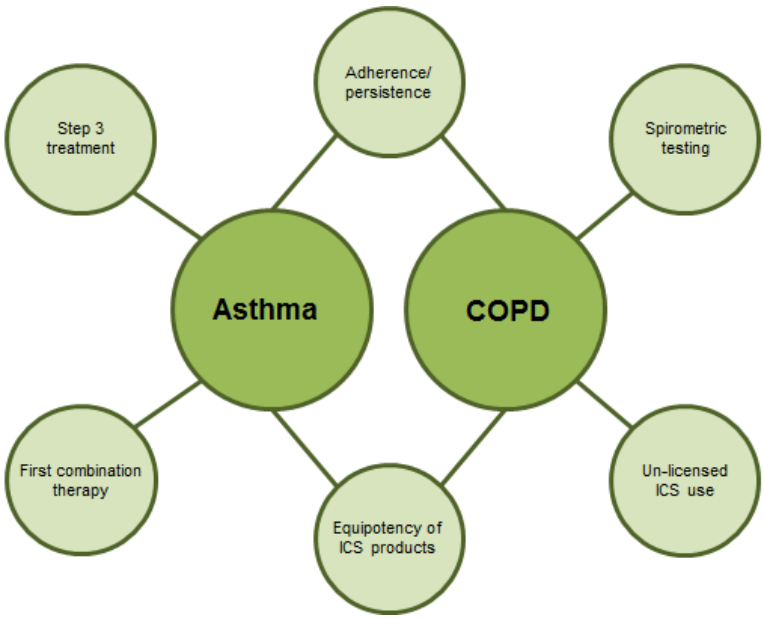


Figure 6.1: Areas identified for quality improvement in respiratory disease

There are several implications of this work in terms of policy and healthcare infrastructure. The descriptive analyses for medicine utilisation in both Scotland as whole and NHS Forth Valley are of interest to the NHS for better understanding of resource allocation, particularly as the use of respiratory medicines and their associated outcomes is common and can incur significant costs. Additionally, how respiratory medicines are being utilised in real world practice completes a 'feedback loop' to bodies such as BTS/SIGN, who consider such emerging data in guideline revisions, and may make evidence-based recommendations which lead to better clinical practice. The corresponding analyses for the KY database showed utilisation at a fraction of the levels in NHS Forth Valley and further research – likely with some incorporation of pharmacoeconomic analysis to account for the hypothesised effect of cost-sharing on medicine utilisation –may be particular pertinent in the era of USA healthcare reform. Demonstration of the enhanced analysis value of EHR data (with the FV database) compared to administrative data (with the KY database) may help to serve as 'proof of purpose' for more integrated systems in the United States. Lastly, the methodology utilised within this work will serve to help future researchers and policy makers to gather and synthesise data to continue informing health care decisions and planning.

6.2 Strengths and limitations of current work

This research had several strengths, namely in its ability to achieve a variety of different goals. First and foremost, the clinical information provided by the analysis of this data was able to inform and provide feedback to the clinician stakeholders in the NHS Forth Valley Airways MCN, which has spurred targeted quality improvement measures within the health board. It has additionally provided stakeholders in Kentucky with some useful comparative data to stimulate further ideas. Secondly, this work trialled the use of several different metrics and sensitivity analyses (e.g. surrogate prevalence markers; DDD vs. aPDD vs. items; persistence windows) and allowed for an evaluation of the pros and cons associated with each method, helping to inform the methodology of continuing work in this area. Lastly, the results also gained academic interest in the wider arena of respiratory disease through peer-reviewed publication, increasing the breadth and dissemination of information.

However, the impact of this body of work must also be considered within the limitations associated with the databases, analyses and subsequent interpretations. The use of medicine utilisation as a marker for determining prevalence (section 3.2) is likely to be a non-sensitive metric for diagnostic surrogacy for a number of disease states (such as asthma) and therefore should be interpreted and utilised with caution. Additionally, the use of the aPDD metric for numerical measurement of medicine utilisation (section 3.3) is generally only applicable to respiratory disease and the use of inhalers, and the raw figures produced from this may be widely different than those for the more recognised DDD metric; this may have potential for confusion in data dissemination and should be noted clearly when communicating figures. For the FV and KY databases (chapters 4 and 5), comparative conclusions drawn from this work must be considered only within the structural constraints of the data as prescribing and dispensing datasets, respectively. Patient populations in either database utilised ‘real world’ samples with limited exclusion criteria that might otherwise be employed in most prospective studies; while this increases the external validity of the work, it does affect the strength of some conclusions. In particular, this may be the case in the FV database where approximately 25% of patients with spirometry failed to meet diagnostic criteria for COPD, or in the KY database where there was significant diagnostic overlap between patients with ICD9-CM codes for

both asthma and COPD. Lastly, data for the FV and KY databases was only available for a three-year time period and therefore only was able to provide a cross-sectional 'snapshot' analysis of prescribing.

6.3 Direction of future research

The present work has utilised routinely collected clinical data to describe, evaluate and stratify patients with respiratory disease in real world practice. Continuing work in this area would ideally follow-up these hypotheses with linkage to outcomes-oriented data, such as accident and emergency visits, hospitalisations and death. Advancement of health data systems within NHS Scotland since this initial data collection in 2007 now enables dataset linkage between primary care, secondary care and pharmacy dispensing datasets, allowing for a more complete evaluation of prescribing and associated outcomes. Of particular interest would be the longer-term disease outcomes with varying levels of adherence and persistence, as well as potential safety outcomes in patients on high doses of ICS. Additionally, this body of database work has generated a number of hypotheses that could be ideally investigated using alternative research methods. The use of an electronic survey was employed amongst clinicians, but structured interviews, focus groups, and content analysis regarding clinician and patient perspectives on medication utilisation in respiratory disease would be an additional area keen for investigation. Lastly, this work was unable to specifically address device-related issues that may significantly influence the results reported with regards to adherence/persistence, such as inhaler technique and difficulty using inhalers; results from this work would indicate this area may also be worthy to pursue.

6.4 Recommendations for future database development

The E-PRS software for the FV database was originally installed to provide clinicians with the ability to audit their own practice-level data to optimise care plans for patients with asthma or COPD. As an EHR dataset, it was more expansive in the types of data collected, although similar to administrative datasets (such as the KY database) the primary goal was not research-minded. As the use of retrospectively collected clinical data for the purpose of research becomes more relevant with national and international healthcare goals, as suggested in the recent national

review of asthma deaths, it is important that several considerations are made with any clinical data project:

(1) *A priori* exploration of potential uses: data designed to be used for multiple purposes simultaneously is highly valuable, as evidenced by the recent developments within NHS Scotland to link datasets from birth to death through the use of the unique CHI number. Purposes certainly extend beyond healthcare and clinical improvement and include resource planning, service forecasting, and benchmarking. Any data collection project should seek to capitalise upon investment and plan for future analysis opportunities from the start, rather than seeking to fit analyses around the available data which can lessen the validity and breadth of the results.

(2) Involvement of clinical stakeholders: due to the current technical expertise required for data collection and analysis tasks related to which health data are captured and how they are handled may be shifted to non-clinical personnel. It is essential that those with the clinical knowledge are either deeply involved in these processes or develop the computational skills to conduct them themselves to ensure the most relevant and useful data. The development and implementation of data analysis tools that are 'friendly' to non-technical staff is the ultimate long-term goal to ensure maximum value from data collection.

(3) Designed to optimise analysis: data are only useful for analysis when stored in a standardised and uniform format, minimising errors, missing data and repetitions. To achieve this, data must be either extensively cleaned after collection, which opens up the possibility for misinterpretation, or designed to store data in the best way possible from initiation (optimally, in a normalised structure). The latter option would be significantly preferred but again requires forethought of the potential uses of data before collection initiates. As important as clinical stakeholders are to the usefulness of data, technical staff are equally necessary to ensure data is worth exploring in the first instance.

(4) Driven by outcomes: describing clinical practice is an important first step to understanding the real world practice of patient care but retrospective analyses from routinely collected data may suffer from a lack of collected outcome data. Inclusion of outcomes data when available greatly increases the utility of data and allows completion of a circle of knowledge in care optimisation.

6.5 Final thoughts

Health services research serves several purposes. In simplest terms the goal is to assess whether therapy prescribed is considered rational (World Health Organization, 2013b). It can relay information regarding whether prescribing advice is utilised by clinicians or describe what the current treatment of asthma or COPD looks like outside of clinical trials and in real practice. In the case of the NHS, it has potential to provide insight into formulary and guideline compliance at the health board level and identify where inefficiencies may be present. This body of work provides a foundation and direction for further intervention-based work to improve the quality of care for patients, as well as areas for development of clinician and patient education. While there are limitations in certain comparisons between the FV and KY databases, the data remain useful when considered independently and provide significant insight into treatment patterns and practices internationally and areas where either country may be able to learn from its counterpart. It is hoped that this work has contributed to the growing body of literature aimed at reducing the burden and improving the quality of care of respiratory disease across the world.

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Appendices

Appendix I: Available data comparison in the FV and KY databases

Selected to fields utilised in performed analyses

Parameter	FV database	KY database
Patient identifier	X	X
Sex	X	X
Age	X	X (year of birth)
Diagnosis	X	X
Diagnosis date	X	
Smoking status/date	X	
FEV_1	X (COPD)	
FVC	X (COPD)	
FEV_1 % predicted	X (COPD)	
Spirometry date	X (COPD)	
Practice identifier	X	
Practice location	X	
Prescription date	X	X
Drug name	X	X
Formulation/strength	X	X
Dose	X	
Frequency	X	
Quantity	X	X
Days supply/interval	X	X
Refill number		X

Appendix II: Ethical approval and data use contracts

University of Strathclyde ethics statement

12th January, 2012.

University of Strathclyde Glasgow

Dr Anne Boyter
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GLASGOW, G4 0RE

Dear Anne,

Project - Comparison of medicine utilisation between the UK and USA respiratory disease population. Student: Jordan Covvey

Just to confirm that the project as described to me, the analysis of anonymised data relating to prescription of medicines in NHS Forth Valley / Kentucky USA, appears to be straight-forward with regard to patient confidentiality . In my opinion, there are not any issues arising that would need to be referred to the University Ethics Committee since patients cannot be individually identified from the database.

I hope this clarifies any issues.

Yours sincerely,

Professor Clive G Wilson,
Representative, Department Ethics Committee (Chair)

File: Ethics 2012

Strathclyde Institute of Pharmacy and Biomedical Sciences
University of Strathclyde
161 Cathedral Street
Glasgow G4 0RE
Scotland

t: 0141 548 2125
f: 0141 552 2562
www.strath.ac.uk/sipbs

NHS contract

National Services Scotland
Human Resources
Gyle Square
1 South Gyle Crescent
EDINBURGH EH12 9EB
Telephone 0131 275 6000
RNID Typetalk: 18001 0131 275 6000
Fax 0131 275 7530
www.nhsnss.org

NHS National Services Scotland

STAFF IN CONFIDENCE

Dr Jordan Covvey
Flat 1/1
34 St Andrews Square
Glasgow
G1 5PP

Date 27th November 2012

Our Ref 10471

Enquiries to Marjory Fraser
Direct Line 0131 275 6131
Email Marjory.fraser@nhs.net

Dear Dr Covvey

RE: Honorary Appointment

I write on behalf of NHS National Services Scotland* to formally offer you an appointment as a **Research Associate** initially with effect from 1st January 2013 until 31st December 2013.

*From now on referred to as the NHS NSS. NHS National Services Scotland is the common name of the Common Services Agency for the Scottish Health Service.

Confidentiality and Disclosure of Information

You may have access to material of a confidential or sensitive nature relating to patients, parents and staff, which should not be divulged to any third party, including NHS Boards/ Trusts, during the period of your honorary contract or any time thereafter without the proper authority having first been given.

You are expected to apply the same standards of care for the confidential data you deal with as would be expected of ISD staff. Therefore you will abide by the standard ISD Confidentiality Rules. This requires you to read, understand and sign an undertaking to abide by these rules at intervals of six months. The translation of certain terms in these Rules is specified in the Annex to this contract.

Role

The main purpose of your role will be to undertake research into the use of medicines in asthma and respiratory disease using data available from the Prescribing Information System (PIS) data warehouse. This will be complimentary to the research being undertaken at the University of Strathclyde for your PhD.

Your pharmaco-epidemiology research using PIS will help to inform ISD of the suitability of the dataset for this type of work and any future development that might be required. You will therefore be expected to develop and maintain appropriate links with relevant Clinical and Analyst staff at ISD and to keep them updated with the progress of your research and any potential issues that you identify.

Notice Period

You will be entitled to receive and are required to give one month notice in writing before the termination of this contract. The contract will be reviewed annually by ISD. This contract will lapse if your tenure with the University of Strathclyde lapses.

POSITIVE ABOUT DISABLED PEOPLE

NHS National Services Scotland

NHS NSS has a duty to ensure so far as is reasonably practicable the health, safety and welfare at work of all its employees.

Every employee/ contractor is also under a duty while at work to take reasonable care for the health and safety of themselves and of others and as regards any duty imposed on NHS NSS to co-operate with the NHS NSS so far as is necessary to enable that duty to be performed or complied with, a copy of the Health and Safety Policy is enclosed.

If you agree to accept this Honorary appointment on the terms specified above, please sign the form of acceptance on both copies of this letter and return one copy to me and retain the second copy for your future reference.

Yours sincerely

MLCatt

PP **Hazel MacKay**
HR Service Centre Manager

ACCEPTANCE CLAUSE

I hereby accept the appointment offered in the foregoing letter on the terms and conditions referred to in it.

Signed _____ **Date** 1/12/2012

This offer and acceptance of it shall together constitute a contract between the parties.

Clinical Data Warehouse Data Use Agreement (DAU)

To: Biomedical Intelligence Reporting Officer

I am requesting access to patient data and/or demographic information, which may include protected health information (PHI) which is housed in the UK Clinical Data Warehouse (CDW). I understand that in order to be granted access to PHI, I must abide by certain requirements in regards to usage, storage, and destruction of any data copied and/or extracted from the CDW as described in the UKHealthcare Policy/Procedure entitled, "Accessing Health Information for Research from the UK Clinical Data Warehouse." I understand the DAU is in effect for the entire length of the research project, regardless of my employment at the University of Kentucky.

I understand that the use of the PHI that I may be granted is restricted to me and the PHI will not be disclosed, loaned, duplicated or shared with any other individual or institution without first securing written permission from the Biomedical Intelligence Reporting Officer.

If employed outside of the covered entity, I understand my data will be released to me on a virtual machine housed on a server within the covered entity, and will not attempt to print, duplicate, disclose, or share any of the information released to me without first securing written permission from the Biomedical Intelligence Reporting Officer.

I have implemented appropriate safeguards to prevent use or disclosure of the PHI to any other entity. Appropriate administrative, technical and physical safeguards including, but not limited to, encryption, password protection, access control, periodic audits, data backup, and virus software have been implemented.

A breach, defined as the acquisition, access, use or disclosure of PHI in a manner not permitted by the HIPAA Privacy Rule, compromises the security and privacy of PHI. Suspected or alleged inappropriate use or disclosure of a patient's PHI must be reported immediately to the UK HealthCare Privacy Officer for investigation. Should a breach occur, I will notify the Biomedical Intelligence Reporting Officer and UKHealthcare Privacy Officer immediately in writing with an accounting of the disclosure of PHI in accordance with 45CFR 164.528.

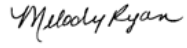
I have taken all appropriate training on HIPAA Privacy & Security, Corporate Compliance which includes Information Technology Security, and Human Subject Protection. Further, I attest I will NOT attempt to re-identify any de-identified data I might receive or in which I am granted access.

I agree to dispose of any and all data stored locally (on my hard drive, temporary storage, or removable media) in accordance with the procedure outlined in the UKHealthcare Policy/Procedure referenced above.

I agree to use the appropriate citation on any publication using data received by the CDW, and I agree to report any publications supported by the CDW upon the request of the Biomedical Intelligence Reporting Officer.

Jordan Covvey, Pharm.D., BCPS
1-18-2012

Requestor's Signature — Print Name — Date
Email: jordan.covvey@uky.edu
Phone: +44 07950611046



Melody Ryan 1/19/12

Sponsoring Faculty Signature — Print Name — Date
[Required for students & non-UK collaborators]
Email: maryan1@email.uky.edu
Phone: 859-257-8790

Tamela Harper

CDW Biomedical Intelligence Reporting Officer's Signature — Print Name — Date
Email: Tamela.Harper@uky.edu
Phone: 257-9384

KY data use agreement, cont.

Researchers' Assurance of *HIPAA* Compliance

I am requesting access to Protected Health Information (PHI) without patient authorization. The research I am conducting is being done in accordance with the guidelines for:

☐ Institutional Review Board (IRB) Waiver - Copy of IRB Waiver and pull list submitted. Researcher agrees to document the review on the Disclosure Tracking form in the medical record.

☐ Preparatory research - Pull list submitted. Researcher agrees to document the review on the Disclosure Tracking form in the medical record.

☐ Decedent research – Pull list submitted and documentation of death must be presented if requested by the covered entity. Researcher agrees to document the review on the Disclosure Tracking form in the medical record.

☐ Research required by law for research or other public health activities – Pull list submitted. Researcher agrees to document the review on the Disclosure Tracking form in the medical record.

☐ Research grandfathered prior to April 14, 2003 – Pull list and informed consent submitted. Researcher will file the informed consent in the patient's medical record.
OR
An IRB approval letter dated prior to April 14, 2003 and a pull list is submitted. Researcher agrees to document the review on the Disclosure Tracking form in the medical record for research grandfathered with an IRB approval letter.

☐ Patient Authorization to Release Information has been obtained – Pull list submitted. Researcher will file the Authorization in the administrative section of the medical record.

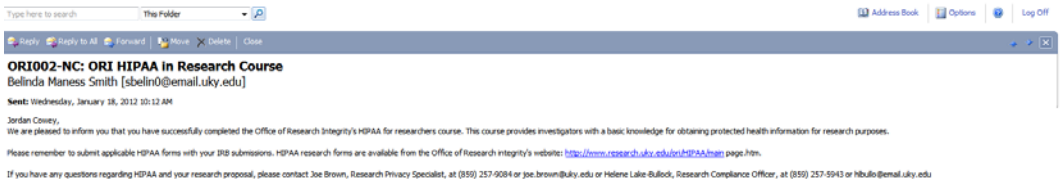
☐ Limited Data Set – Pull list submitted. Data Use Agreement and a Business Associate Agreement have been obtained.

X De-identified Data research - De-identification Certification Form and pull list submitted. Information released to the researcher must be limited to the data requested with the Certification Form.

1. I assure that use or disclosure is solely for research.
2. I assure that PHI is necessary for research purposes and only the minimum amount of PHI will be reviewed for the study.
3. I assure that no PHI will be removed from the covered entity.
4. I agree to follow the documentation requirements outlined above for this research project.

Prescribing outcomes in respiratory medicine patients in the UK and USA	Pharmacoepidemiological study on COPD patients from disease registers in Scotland and Kentucky
Name of Research Study	**Brief Description of Research**
[signature]	1-18-2012
Signature of Researcher	**Date**
External collaborator	Pharmacy +44 07590611046
Title	**Department** **Phone number**

KY HIPAA and researcher training



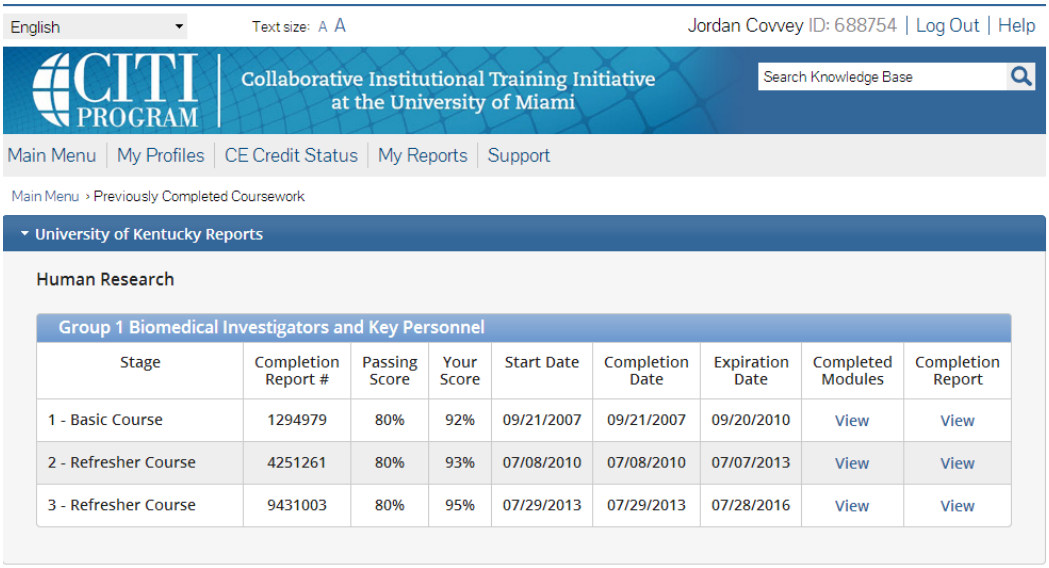
ORI002-NC: ORI HIPAA in Research Course
Belinda Maness Smith [sbelin0@email.uky.edu]

Sent: Wednesday, January 18, 2012 10:12 AM

Jordan Cowey,
We are pleased to inform you that you have successfully completed the Office of Research Integrity's HIPAA for researchers course. This course provides investigators with a basic knowledge for obtaining protected health information for research purposes.

Please remember to submit applicable HIPAA forms with your IRB submissions. HIPAA research forms are available from the Office of Research Integrity's website: http://www.research.uky.edu/ori/HIPAA/main page.htm.

If you have any questions regarding HIPAA and your research proposal, please contact Joe Brown, Research Privacy Specialist, at (859) 257-9084 or joe.brown@uky.edu or Helene Lake-Bullock, Research Compliance Officer, at (859) 257-5943 or hlbullo@email.uky.edu



English Text size: A A Jordan Covvey ID: 688754 | Log Out | Help

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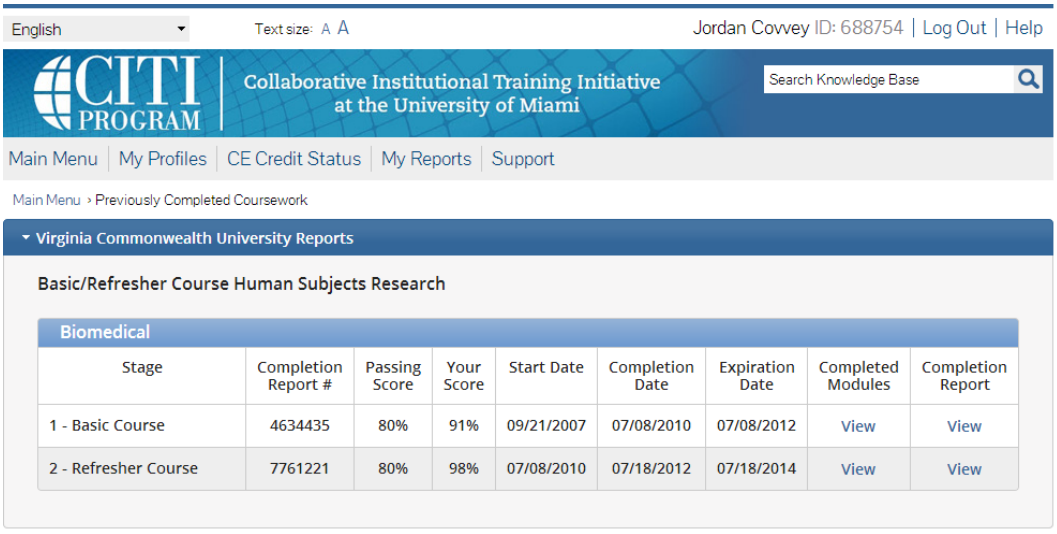
University of Kentucky Reports

Human Research

Group 1 Biomedical Investigators and Key Personnel

Stage	Completion Report #	Passing Score	Your Score	Start Date	Completion Date	Expiration Date	Completed Modules	Completion Report
1 - Basic Course	1294979	80%	92%	09/21/2007	09/21/2007	09/20/2010	View	View
2 - Refresher Course	4251261	80%	93%	07/08/2010	07/08/2010	07/07/2013	View	View
3 - Refresher Course	9431003	80%	95%	07/29/2013	07/29/2013	07/28/2016	View	View



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Virginia Commonwealth University Reports

Basic/Refresher Course Human Subjects Research

Biomedical

Stage	Completion Report #	Passing Score	Your Score	Start Date	Completion Date	Expiration Date	Completed Modules	Completion Report
1 - Basic Course	4634435	80%	91%	09/21/2007	07/08/2010	07/08/2012	View	View
2 - Refresher Course	7761221	80%	98%	07/08/2010	07/18/2012	07/18/2014	View	View

Appendix III: Sample SQL queries

1

```
SELECT DISTINCT PracticeID, Datazone, MAX(TotalPopulation)
FROM (SELECT DISTINCT tbl_practice_imports.PracticeID, tbl_practices.Datazone,
tbl_practice_imports.TotalPopulation
FROM tbl_practice_imports INNER JOIN
tbl_practices ON tbl_practice_imports.PracticeID = tbl_practices.ID
WHERE YEAR(ExportDate) >= '2009') AS table1
GROUP BY PracticeID, Datazone
ORDER BY Datazone, PracticeID
```

2

```
SELECT DISTINCT PracticeID, Datazone, COUNT(PatientID)
FROM (SELECT DISTINCT tbl_practices.Datazone,
tbl_asthma_prescriptions_3_stepdate.PracticeID,
tbl_asthma_prescriptions_3_stepdate.PatientID
FROM tbl_practices INNER JOIN tbl_asthma_prescriptions_3_stepdate
ON tbl_practices.ID = tbl_asthma_prescriptions_3_stepdate.PracticeID
WHERE YEAR(DateIssued) >= '2009' AND
(DrugName LIKE 'beclo%' OR DrugName LIKE 'budes%' OR DrugName LIKE 'clenil%'
OR DrugName LIKE 'flutic%' OR DrugName LIKE 'qvar%' OR DrugName LIKE
'seretide%' OR DrugName LIKE 'symbi%')) AS table1
GROUP BY PracticeID, Datazone
ORDER BY Datazone, PracticeID
```

3

```
SELECT DISTINCT PracticeID, Datazone, COUNT(PatientID)
FROM (SELECT DISTINCT tbl_practices.Datazone,
tbl_copd_prescriptions.PracticeID, tbl_copd_prescriptions.PatientID
FROM tbl_practices INNER JOIN tbl_copd_prescriptions
ON tbl_practices.ID = tbl_copd_prescriptions.PracticeID
WHERE YEAR(DateIssued) >= '2009' AND
DrugName LIKE 'tiotrop%') AS table1
GROUP BY PracticeID, Datazone
ORDER BY Datazone, PracticeID
```

4

```
SELECT derivedtbl_1.PracticeID, derivedtbl_1.PatientID,
(2007 - DOB) AS Age
FROM (SELECT DISTINCT PracticeID, PatientID
FROM tbl_asthma_prescriptions_3
WHERE (YEAR(DateIssued) = '2007')) AS derivedtbl_1 INNER JOIN
(SELECT TOP (100) PERCENT PracticeID, PatientID, AVG(DOB) AS DOB
FROM (SELECT DISTINCT tbl_practice_imports.PracticeID,
tbl_asthma_data.PatientID, tbl_asthma_data.Sex, tbl_asthma_data.AgeInYears,
tbl_practice_imports.ExportDate, YEAR(tbl_practice_imports.ExportDate) –
tbl_asthma_data.AgeInYears AS DOB
FROM tbl_asthma_data INNER JOIN tbl_practice_imports
ON tbl_asthma_data.importid = tbl_practice_imports.ID) AS derivedtbl_1_1
GROUP BY PracticeID, PatientID
ORDER BY PracticeID, PatientID) AS derivedtbl_2
ON derivedtbl_1.PracticeID = derivedtbl_2.PracticeID AND
derivedtbl_1.PatientID = derivedtbl_2.PatientID
```

5

```
SELECT DISTINCT Indicator.PATID, Overall.GDR_CD,
(2007 - Demographics.YRDOB) AS Age
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID INNER JOIN Demographics
ON Demographics.PATID = Overall.PATID INNER JOIN Prescriptions
ON Prescriptions.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND
DATEPART(year, Prescriptions.FILL_DT) = '2007'
```

6

```
SELECT *
FROM tbl_asthma_prescriptions_3_stepdate
WHERE (YEAR(DateIssued) = '2009' OR YEAR(DateIssued) = '2008' OR
YEAR(DateIssued) = '2007') AND  (DrugName LIKE 'salbutamol%' OR DrugName LIKE
'terbut%' OR DrugName LIKE 'beclo%' OR DrugName LIKE 'budes%' OR DrugName LIKE
'clenil%' OR DrugName LIKE 'flutica%' OR DrugName LIKE 'qvar%' OR  DrugName
LIKE 'cicles%' OR DrugName LIKE 'mometa%' OR DrugName LIKE 'seretide%' OR
DrugName LIKE 'symbi%' OR DrugName LIKE 'salmeter%' OR DrugName LIKE
'formoter%' OR DrugName LIKE 'amino%' OR DrugName LIKE 'uniphyl%' OR DrugName
LIKE 'theophyl%' OR DrugName LIKE 'slophyl%' OR DrugName LIKE 'phyllo%' OR
DrugName LIKE 'prednis%')
```

7

```
SELECT DISTINCT PracticeID, PatientID
FROM tbl_asthma_prescriptions_3_stepdate
WHERE (YEAR(DateIssued) = '2009' OR YEAR(DateIssued) = '2008' OR
YEAR(DateIssued) = '2007') AND (DrugName LIKE 'salbutamol%' OR DrugName LIKE
'terbut%' OR DrugName LIKE 'beclo%' OR DrugName LIKE 'budes%' OR DrugName LIKE
'clenil%' OR DrugName LIKE 'flutica%' OR DrugName LIKE 'qvar%' OR  DrugName
LIKE 'cicles%' OR DrugName LIKE 'mometa%' OR DrugName LIKE 'seretide%' OR
DrugName LIKE 'symbi%' OR DrugName LIKE 'salmeter%' OR DrugName LIKE
'formoter%' OR DrugName LIKE 'amino%' OR DrugName LIKE 'uniphyl%' OR DrugName
LIKE 'theophyl%' OR DrugName LIKE 'slophyl%' OR DrugName LIKE 'phyllo%' OR
DrugName LIKE 'prednis%')
```

8

```
SELECT *
FROM Prescriptions_clean INNER JOIN Indicator
ON Prescriptions_clean.PATID = Indicator.PATID
WHERE (YEAR(FILL_DT) = '2009') AND  (Indicator.Asthma = 1) AND
(BRND_NM LIKE 'Accuneb%' OR BRND_NM LIKE 'Albuterol%' OR BRND_NM LIKE
'maxair%' OR BRND_NM LIKE 'proair%' OR BRND_NM LIKE 'ventolin%' OR BRND_NM
LIKE 'xopenex%' OR BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%' OR
BRND_NM LIKE 'azmacort%' OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE 'pulmicort
flexhaler%' OR BRND_NM LIKE 'budesonide%' OR BRND_NM LIKE 'pulmicort  %' OR
BRND_NM LIKE 'qvar%' OR BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%' OR
BRND_NM LIKE 'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE
'perforomist%' OR BRND_NM LIKE 'serevent%' OR BRND_NM LIKE 'elixophyllin%' OR
BRND_NM LIKE 'theo%' OR BRND_NM LIKE 'zyflo%' OR BRND_NM LIKE 'singulair%' OR
BRND_NM LIKE 'accolate%')
```

9

```
SELECT DISTINCT Prescriptions_clean.PATID
FROM Prescriptions_clean INNER JOIN Indicator
ON Prescriptions_clean.PATID = Indicator.PATID
WHERE (YEAR(FILL_DT) = '2009') AND  (Indicator.Asthma = 1) AND
(BRND_NM LIKE 'Accuneb%' OR BRND_NM LIKE 'Albuterol%' OR BRND_NM LIKE
'maxair%' OR BRND_NM LIKE 'proair%' OR BRND_NM LIKE 'ventolin%' OR BRND_NM
LIKE 'xopenex%' OR BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%' OR
BRND_NM LIKE 'azmacort%' OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE 'pulmicort
flexhaler%' OR BRND_NM LIKE 'budesonide%' OR BRND_NM LIKE 'pulmicort  %' OR
BRND_NM LIKE 'qvar%' OR BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%' OR
BRND_NM LIKE 'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE
'perforomist%' OR BRND_NM LIKE 'serevent%' OR BRND_NM LIKE 'elixophyllin%' OR
BRND_NM LIKE 'theo%' OR BRND_NM LIKE 'zyflo%' OR BRND_NM LIKE 'singulair%' OR
BRND_NM LIKE 'accolate%')
```

10

```
SELECT DrugName, Preparation,
SUM(DosesPerInhaler * Quantity *NumberRxs) AS Total
FROM (SELECT DrugName, Preparation, DosesPerInhaler, Quantity,
COUNT(DateIssued) AS NumberRxs
FROM (SELECT DISTINCT PracticeID, PatientID, PrescriptionID, DrugName,
Preparation, Dose, DosesPerInhaler, Frequency, Quantity, PrescriptionInterval,
DateIssued
FROM tbl_asthma_prescriptions_3_step
WHERE YEAR(DateIssued) = '2008' AND MONTH(DateIssued) = '01' AND
(DrugName LIKE 'salbut%') AND (DosesPerInhaler IS NOT NULL) AND
AgeOnPrescription > 12 ) AS derivedtbl_1_1
GROUP BY DrugName, Preparation, DosesPerInhaler, Quantity)
AS derivedtbl_1
GROUP BY DrugName, Preparation
ORDER BY DrugName, Preparation

SELECT DISTINCT PracticeID, PatientID
FROM (SELECT DISTINCT PracticeID, PatientID, PrescriptionID, DrugName,
Preparation, DosesPerInhaler, Dose, Frequency, Quantity, PrescriptionInterval,
DateIssued
FROM tbl_asthma_prescriptions_3_step
WHERE YEAR(DateIssued) = '2008' AND MONTH(DateIssued) = '01' AND
(DrugName LIKE 'salbut%') AND DosesPerInhaler IS NOT NULL
AND AgeOnPrescription > 12 ) AS derivedtbl_1
```

11

```
SELECT DISTINCT BRND_NM, STRENGTH,
SUM(InhalerQuantity * NumberRxs * DosesPerInhaler) as NumberDoses
FROM (SELECT DISTINCT BRND_NM, STRENGTH, InhalerQuantity, DosesPerInhaler,
COUNT(FILL_DT) AS NumberRxs
FROM (SELECT Prescriptions_clean.PATID, BRND_NM, STRENGTH, QUANTITY, DAYS_SUP,
FILL_DT, McgPerDay, DosesPerInhaler, InhalerQuantity FROM Indicator INNER JOIN
Overall ON Indicator.PATID = Overall.PATID INNER JOIN Prescriptions_clean ON
```

```
Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND YEAR(Prescriptions_clean.FILL_DT) = '2008'
AND MONTH(Prescriptions_clean.FILL_DT) = '01' AND
(2008 - Overall.YRDOB) > 12 AND
(BRND_NM LIKE 'albuterol%')) AS table1
GROUP BY BRND_NM, STRENGTH, InhalerQuantity, DosesPerInhaler) AS table2
GROUP BY BRND_NM, STRENGTH

SELECT DISTINCT table1.PATID
FROM (SELECT Prescriptions_clean.PATID, BRND_NM, STRENGTH, QUANTITY, DAYS_SUP,
FILL_DT, McgPerDay, DosesPerInhaler FROM Indicator INNER JOIN Overall ON
Indicator.PATID = Overall.PATID INNER JOIN Prescriptions_clean ON
Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND YEAR(Prescriptions_clean.FILL_DT) = '2008'
AND MONTH(Prescriptions_clean.FILL_DT) = '01' AND
(2008 - Overall.YRDOB) > 12 AND (BRND_NM LIKE 'albuterol%')) AS table1
```

12

```
SELECT DISTINCT PracticeID, PatientID, PrescriptionID, DrugName, Preparation,
Dose, McgPerDay, Frequency, Quantity, PrescriptionInterval, DateIssued
FROM tbl_asthma_prescriptions_3_step
WHERE YEAR(DateIssued) = '2008' AND MONTH(DateIssued) = '01' AND
(DrugName LIKE 'beclom%') AND (AgeOnPrescription > 12)
ORDER BY Preparation
```

13

```
SELECT Prescriptions_clean.PATID, BRND_NM, STRENGTH, QUANTITY, DAYS_SUP,
FILL_DT, McgPerDay, DosesPerInhaler
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND YEAR(Prescriptions_clean.FILL_DT) = '2009'
AND MONTH(Prescriptions_clean.FILL_DT) = '01' AND (2008 - Overall.YRDOB) > 12
AND BRND_NM LIKE '[insert]'
```

14

```
CREATE TABLE #MPRAsthma
(PracticeID int, PatientID int, Num float, Denom float, MPR float)
INSERT INTO #MPRASthma (PracticeID, PatientID, Num, Denom, MPR)
SELECT DISTINCT PracticeID, PatientID, Num, Denom,
(Num-PrescriptionInterval)/Denom AS MPR
FROM (SELECT DISTINCT PracticeID, PatientID, Num, MIN(PrescriptionInterval) AS
PrescriptionInterval, Denom
FROM (SELECT derivedtbl_3.PracticeID, derivedtbl_3.PatientID,
derivedtbl_3.Num, derivedtbl_3.Denom, derivedtbl_1.PrescriptionInterval
FROM (SELECT DISTINCT derivedtbl_1_1.PracticeID, derivedtbl_1_1.PatientID,
derivedtbl_1_1.LastRank, derivedtbl_2.PrescriptionInterval
FROM (SELECT PracticeID, PatientID, MAX(RowNumberClass) AS LastRank
FROM  tbl_asthma_prescriptions_3_stepdate
WHERE (YEAR(DateIssued) = '2007' OR YEAR(DateIssued) = '2009' OR
YEAR(DateIssued) = '2008') AND
(DrugName = 'Beclometasone' OR DrugName = 'Budesonide' OR DrugName LIKE
'Clenil%' OR DrugName LIKE 'Fluticasone%' OR DrugName LIKE 'Qvar%')
GROUP BY PracticeID, PatientID) AS derivedtbl_1_1 INNER JOIN
(SELECT PracticeID, PatientID, DrugName, Preparation, PrescriptionInterval,
RowNumberClass
FROM tbl_asthma_prescriptions_3_stepdate AS
tbl_asthma_prescriptions_3_stepdate_1
WHERE (YEAR(DateIssued) = '2007' OR YEAR(DateIssued) = '2009' OR
YEAR(DateIssued) = '2008') AND
(DrugName = 'Beclometasone' OR DrugName = 'Budesonide' OR DrugName LIKE
'Clenil%' OR DrugName LIKE 'Fluticasone%' OR DrugName LIKE 'Qvar%')) AS
derivedtbl_2 ON derivedtbl_1_1.PracticeID = derivedtbl_2.PracticeID AND
derivedtbl_1_1.PatientID = derivedtbl_2.PatientID AND
derivedtbl_1_1.LastRank = derivedtbl_2.RowNumberClass) AS derivedtbl_1
INNER JOIN (SELECT PracticeID, PatientID, Num, Denom
FROM (SELECT PracticeID, PatientID, CAST(SUM(PrescriptionInterval) AS float)
AS Num, CAST(MAX(DaysSinceIndex) - MIN(DaysSinceIndex) AS float) AS Denom
FROM (SELECT derivedtbl_1_2.PracticeID, derivedtbl_1_2.PatientID,
derivedtbl_2_1.IndexDate, derivedtbl_1_2.DateIssued,
DATEDIFF(day, derivedtbl_2_1.IndexDate, derivedtbl_1_2.DateIssued) AS
DaysSinceIndex, DATEDIFF(DAY, derivedtbl_1_2.PreviousDateIssuedClass,
derivedtbl_1_2.DateIssued) AS DaysSinceLast, DATEDIFF(day,
derivedtbl_1_2.DateIssued,
derivedtbl_1_2.NextDateIssuedClass) AS DaysToNext,
derivedtbl_1_2.PrescriptionInterval, derivedtbl_1_2.McgPerDayAdj,
derivedtbl_1_2.DateRank
```

```
FROM (SELECT PracticeID, PatientID, PrescriptionID, AgeOnPrescription,
DateIssued, PreviousDateIssuedClass, NextDateIssuedClass, DrugName,
Preparation, Dose, Frequency, Quantity, PrescriptionInterval, DosesPerInhaler,
McgPerDayAdj, DateRank
FROM tbl_asthma_prescriptions_3_stepdate AS
tbl_asthma_prescriptions_3_stepdate_2
WHERE (YEAR(DateIssued) = '2007' OR YEAR(DateIssued) = '2009' OR
YEAR(DateIssued) = '2008') AND
(DrugName = 'Beclometasone' OR DrugName = 'Budesonide' OR DrugName LIKE
'Clenil%' OR DrugName LIKE 'Fluticasone%' OR DrugName LIKE 'Qvar%')) AS
derivedtbl_1_2 INNER JOIN
(SELECT DISTINCT PracticeID, PatientID, MIN(DateIssued) AS IndexDate
FROM (SELECT DISTINCT PracticeID, PatientID, DateIssued
FROM tbl_asthma_prescriptions_3_step AS tbl_asthma_prescriptions_3_step_1
WHERE (YEAR(DateIssued) = '2007' OR YEAR(DateIssued) = '2009' OR
YEAR(DateIssued) = '2008') AND
(DrugName = 'Beclometasone' OR DrugName = 'Budesonide' OR DrugName LIKE
'Clenil%' OR DrugName LIKE 'Fluticasone%' OR DrugName LIKE 'Qvar%')) AS table1
GROUP BY PracticeID, PatientID) AS derivedtbl_2_1
ON derivedtbl_1_2.PracticeID = derivedtbl_2_1.PracticeID AND
derivedtbl_1_2.PatientID = derivedtbl_2_1.PatientID AND
derivedtbl_1_2.DateIssued >= derivedtbl_2_1.IndexDate) AS table2
GROUP BY PracticeID, PatientID
HAVING (MAX(DaysSinceIndex) - MIN(DaysSinceIndex) > '0')) AS table3) AS
derivedtbl_3 ON derivedtbl_1.PracticeID = derivedtbl_3.PracticeID AND
derivedtbl_1.PatientID = derivedtbl_3.PatientID) AS table4
GROUP BY PracticeID, PatientID, Num, Denom) AS table5
ORDER BY PracticeID, PatientID
SELECT DISTINCT table2.PracticeID, table2.PatientID, Sex,
(2007-DOB) AS Age, MPR
FROM (SELECT DISTINCT PracticeID, PatientID, MPR
FROM (SELECT DISTINCT #MPRAsthma.PracticeID, #MPRAsthma.PatientID, MPR,
COPD = CASE WHEN tableCOPD.PracticeID > 0 THEN 1 END
FROM #MPRAsthma LEFT JOIN
(SELECT DISTINCT tbl_practice_imports.PracticeID, tbl_copd_data.PatientID
FROM tbl_copd_data INNER JOIN tbl_practice_imports ON tbl_copd_data.importid =
tbl_practice_imports.ID) AS tableCOPD
ON #MPRAsthma.PracticeID = tableCOPD.PracticeID AND #MPRAsthma.PatientID =
tableCOPD.PatientID) AS table1
WHERE COPD IS NULL) AS table2 LEFT JOIN
(SELECT DISTINCT PracticeID, PatientID, Sex, AVG(DOB) AS DOB
FROM (SELECT DISTINCT tbl_practice_imports.PracticeID,
tbl_asthma_data.PatientID, tbl_asthma_data.Sex, tbl_asthma_data.AgeInYears,
tbl_practice_imports.ExportDate, YEAR(tbl_practice_imports.ExportDate) -
tbl_asthma_data.AgeInYears AS DOB
FROM tbl_asthma_data INNER JOIN tbl_practice_imports
ON tbl_asthma_data.importid = tbl_practice_imports.ID) AS derivedtbl_1_1
GROUP BY PracticeID, PatientID, Sex) AS table3
ON table2.PracticeID = table3.PracticeID AND table2.PatientID =
table3.PatientID
ORDER BY table2.PracticeID, table2.PatientID
DROP TABLE #MPRAsthma
```

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```
SELECT DISTINCT PATID, Age, GDR_CD, Num, DAYS_SUP, Denom, (Num-DAYS_SUP)/Denom
AS MPR
FROM (SELECT derivedtbl_3.PATID, Age, GDR_CD, derivedtbl_3.Num,
derivedtbl_3.Denom, derivedtbl_1.DAYS_SUP
FROM (SELECT DISTINCT derivedtbl_1_1.PATID, derivedtbl_1_1.LastRank,
derivedtbl_2.Age,derivedtbl_2.GDR_CD, derivedtbl_2.DAYS_SUP
FROM  (SELECT TOP (100) PERCENT Indicator.PATID, Class, MAX(RowNumberClass) AS
LastRank
FROM Indicator INNER JOIN Overall ON Indicator.PATID = Overall.PATID
INNER JOIN Demographics ON Demographics.PATID = Overall.PATID
INNER JOIN Prescriptions_clean ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1 AND Indicator.COPD = 0 AND
Indicator.Chronic_bronchitis = 0 AND Indicator.Emphysema = 0)
AND (YEAR(FILL_DT) = '2008' OR YEAR(FILL_DT) = '2009') AND
(BRND_NM LIKE 'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM LIKE
'zyflo%')
GROUP BY Indicator.PATID, Class) AS derivedtbl_1_1 INNER JOIN
(SELECT TOP (100) PERCENT Indicator.PATID, Demographics.GDR_CD, (2007 -
Demographics.YRDOB) AS Age, BRND_NM, STRENGTH, DAYS_SUP, Class, RowNumberClass
FROM Indicator INNER JOIN Overall ON Indicator.PATID = Overall.PATID
INNER JOIN Demographics ON Demographics.PATID = Overall.PATID
```

```
INNER JOIN Prescriptions_clean ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1 AND Indicator.COPD = 0 AND
Indicator.Chronic_bronchitis = 0 AND Indicator.Emphysema = 0)
AND (YEAR(FILL_DT) = '2008' OR YEAR(FILL_DT) = '2009') AND
(BRND_NM LIKE 'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM LIKE
'zyflo%')) AS derivedtbl_2
ON derivedtbl_1_1.PATID = derivedtbl_2.PATID AND
derivedtbl_1_1.Class = derivedtbl_2.Class AND
derivedtbl_1_1.LastRank = derivedtbl_2.RowNumberClass) AS derivedtbl_1 INNER
JOIN (SELECT PATID, Num, Denom
FROM (SELECT DISTINCT PATID, CAST(SUM(DAYS_SUP) AS float) AS Num,
CAST((MAX(DaysSinceIndex) - MIN(DaysSinceIndex)) AS float) AS Denom
FROM (SELECT DISTINCT table1.PATID, IndexDate, table1.Class, FILL_DT,
DATEDIFF(day, IndexDate, FILL_DT) AS DaysSinceIndex, DATEDIFF(DAY,
PreviousDateIssuedClass, FILL_DT) AS DaysSinceLast,
DATEDIFF(day, FILL_DT, NextDateIssuedClass) AS DaysToNext, BRND_NM, STRENGTH,
QUANTITY, DAYS_SUP, McgPerDay, RowNumberClass
FROM (SELECT DISTINCT Indicator.PATID, Overall.GDR_CD, (2009 -
Demographics.YRDOB) AS Age, BRND_NM, STRENGTH, DAYS_SUP, QUANTITY, McgPerDay,
DosesPerInhaler, InhalerQuantity, FILL_DT, Class, RowNumberClass,
PreviousDateIssuedClass, NextDateIssuedClass
FROM Indicator INNER JOIN Overall ON Indicator.PATID = Overall.PATID
INNER JOIN Demographics ON Demographics.PATID = Overall.PATID
INNER JOIN Prescriptions_clean ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1 AND Indicator.COPD = 0 AND
Indicator.Chronic_bronchitis = 0 AND Indicator.Emphysema = 0)
AND (YEAR(FILL_DT) = '2008' OR YEAR(FILL_DT) = '2009') AND
(BRND_NM LIKE 'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM LIKE
'zyflo%')) AS table1 INNER JOIN
(SELECT DISTINCT PATID, Class, MIN(FILL_DT) AS IndexDate
FROM (SELECT DISTINCT Indicator.PATID, Overall.GDR_CD, (2007 -
Demographics.YRDOB) AS Age, Prescriptions_clean.FILL_DT, Class
FROM Indicator INNER JOIN Overall ON Indicator.PATID = Overall.PATID
INNER JOIN Demographics ON Demographics.PATID = Overall.PATID
INNER JOIN Prescriptions_clean ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1 AND Indicator.COPD = 0 AND
Indicator.Chronic_bronchitis = 0 AND Indicator.Emphysema = 0) AND
(YEAR(FILL_DT) = '2008' OR YEAR(FILL_DT) = '2009') AND
(BRND_NM LIKE 'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM LIKE
'zyflo%')) AS table1
GROUP BY PATID, Class) AS table2
ON table1.PATID = table2.PATID AND table1.Class = table2.Class
WHERE FILL_DT >= IndexDate) AS table3
GROUP BY PATID
HAVING (MAX(DaysSinceIndex) - MIN(DaysSinceIndex)) > '0') AS table4) AS
derivedtbl_3
ON derivedtbl_1.PATID = derivedtbl_3.PATID) AS table4
ORDER BY PATID
```

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```
CREATE TABLE #MPRAsthma
(PracticeID int, PatientID int, IndexDate datetime, Num float, Denom float,
MPR float)
INSERT INTO #MPRASthma (PracticeID, PatientID, IndexDate, Num, Denom, MPR)
SELECT DISTINCT PracticeID, PatientID, IndexDate, Num, Denom, (Num-
PrescriptionInterval)/Denom AS MPR
FROM (SELECT DISTINCT PracticeID, PatientID, IndexDate, Num,
MIN(PrescriptionInterval) AS PrescriptionInterval, Denom
FROM (SELECT derivedtbl_3.PracticeID, derivedtbl_3.IndexDate,
derivedtbl_3.PatientID, derivedtbl_3.Num, derivedtbl_3.Denom,
derivedtbl_1.PrescriptionInterval
FROM (SELECT DISTINCT derivedtbl_1_1.PracticeID, derivedtbl_1_1.PatientID,
derivedtbl_1_1.LastRank, derivedtbl_2.PrescriptionInterval
FROM (SELECT PracticeID, PatientID, MAX(RowNumberClass) AS LastRank
FROM  tbl_asthma_prescriptions_3_stepdate
WHERE (YEAR(DateIssued) = '2009' OR YEAR(DateIssued) = '2008' OR
YEAR(DateIssued) = '2007') AND  (DrugName LIKE 'seretide%' OR DrugName LIKE
'symbi%')
GROUP BY PracticeID, PatientID) AS derivedtbl_1_1 INNER JOIN
(SELECT PracticeID, PatientID, DrugName, Preparation, PrescriptionInterval,
RowNumberClass
FROM tbl_asthma_prescriptions_3_stepdate AS
tbl_asthma_prescriptions_3_stepdate_1
WHERE (YEAR(DateIssued) = '2009' OR YEAR(DateIssued) = '2008' OR
YEAR(DateIssued) = '2007') AND (DrugName LIKE 'seretide%' OR DrugName LIKE
```

```
'symbi%')) AS derivedtbl_2 ON derivedtbl_1_1.PracticeID =
derivedtbl_2.PracticeID AND derivedtbl_1_1.PatientID = derivedtbl_2.PatientID
AND derivedtbl_1_1.LastRank = derivedtbl_2.RowNumberClass) AS derivedtbl_1
INNER JOIN
(SELECT PracticeID, PatientID, IndexDate, Num, Denom
FROM (SELECT PracticeID, PatientID, IndexDate, CAST(SUM(PrescriptionInterval)
AS float) AS Num, CAST(MAX(DaysSinceIndex) - MIN(DaysSinceIndex) AS float) AS
Denom
FROM (SELECT derivedtbl_1_2.PracticeID, derivedtbl_1_2.PatientID,
derivedtbl_2_1.IndexDate, derivedtbl_1_2.DateIssued,
DATEDIFF(day, derivedtbl_2_1.IndexDate, derivedtbl_1_2.DateIssued) AS
DaysSinceIndex, DATEDIFF(DAY, derivedtbl_1_2.PreviousDateIssuedClass,
derivedtbl_1_2.DateIssued) AS DaysSinceLast, DATEDIFF(day,
derivedtbl_1_2.DateIssued,
derivedtbl_1_2.NextDateIssuedClass) AS DaysToNext,
derivedtbl_1_2.PrescriptionInterval, derivedtbl_1_2.McgPerDayAdj,
derivedtbl_1_2.DateRank
FROM (SELECT PracticeID, PatientID, PrescriptionID, AgeOnPrescription,
DateIssued, PreviousDateIssuedClass, NextDateIssuedClass, DrugName,
Preparation, Dose, Frequency, Quantity, PrescriptionInterval, DosesPerInhaler,
McgPerDayAdj, DateRank
FROM tbl_asthma_prescriptions_3_stepdate AS
tbl_asthma_prescriptions_3_stepdate_2
WHERE (YEAR(DateIssued) = '2009' OR YEAR(DateIssued) = '2008' OR
YEAR(DateIssued) = '2007') AND (DrugName LIKE 'seretide%' OR DrugName LIKE
'symbi%')) AS derivedtbl_1_2 INNER JOIN
(SELECT DISTINCT PracticeID, PatientID, MIN(DateIssued) AS IndexDate
FROM (SELECT DISTINCT PracticeID, PatientID, DateIssued
FROM tbl_asthma_prescriptions_3_step AS tbl_asthma_prescriptions_3_step_1
WHERE (YEAR(DateIssued) = '2009' OR YEAR(DateIssued) = '2008' OR
YEAR(DateIssued) = '2007') AND  (DrugName LIKE 'seretide%' OR DrugName LIKE
'symbi%')) AS table1
GROUP BY PracticeID, PatientID) AS derivedtbl_2_1
ON derivedtbl_1_2.PracticeID = derivedtbl_2_1.PracticeID AND
derivedtbl_1_2.PatientID = derivedtbl_2_1.PatientID AND
derivedtbl_1_2.DateIssued >= derivedtbl_2_1.IndexDate) AS table2
GROUP BY PracticeID, PatientID, IndexDate
HAVING (MAX(DaysSinceIndex) - MIN(DaysSinceIndex) > '7')) AS table3) AS
derivedtbl_3 ON derivedtbl_1.PracticeID = derivedtbl_3.PracticeID AND
derivedtbl_1.PatientID = derivedtbl_3.PatientID) AS table4
GROUP BY PracticeID, PatientID, IndexDate, Num, Denom) AS table5
ORDER BY PracticeID, PatientID
SELECT DISTINCT PracticeID, PatientID, MPR,
(SUM(DosesPerInhaler*Quantity*COUNT))/Denom AS DosesPerDay
FROM (SELECT DISTINCT PracticeID, PatientID, MPR, Denom, DosesPerInhaler,
Quantity, COUNT(DateIssued) AS COUNT
FROM (SELECT DISTINCT table2.PracticeID, table2.PatientID, MPR, Denom,
IndexDate, EndDate, DosesPerInhaler, Quantity, DateIssued
FROM (SELECT DISTINCT PracticeID, PatientID, MPR, IndexDate, Denom,
DATEADD(day, Denom, IndexDate) AS EndDate
FROM (SELECT DISTINCT #MPRAsthma.PracticeID, #MPRAsthma.PatientID, IndexDate,
Denom, MPR, COPD = CASE WHEN
tableCOPD.PracticeID > 0 THEN 1 END
FROM #MPRAsthma LEFT JOIN
(SELECT DISTINCT tbl_practice_imports.PracticeID, tbl_copd_data.PatientID
FROM tbl_copd_data INNER JOIN tbl_practice_imports ON tbl_copd_data.importid =
tbl_practice_imports.ID) AS tableCOPD
ON #MPRAsthma.PracticeID = tableCOPD.PracticeID AND #MPRAsthma.PatientID =
tableCOPD.PatientID) AS table1
WHERE COPD IS NULL) AS table2 LEFT JOIN
(SELECT DISTINCT PracticeID, PatientID, DosesPerInhaler, Quantity, DateIssued
FROM tbl_asthma_prescriptions_3_stepdate
WHERE (DrugName LIKE 'salbut%' OR DrugName LIKE 'terbut%')) AS table3
ON table2.PracticeID = table3.PracticeID AND table2.PatientID =
table3.PatientID
WHERE DateIssued >= IndexDate AND DateIssued <= EndDate) AS table4
GROUP BY PracticeID, PatientID, MPR, Denom, DosesPerInhaler, Quantity) AS
table5
GROUP BY PracticeID, PatientID, MPR, Denom
DROP TABLE #MPRAsthma
```

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```
CREATE TABLE #KM
(PracticeID int, PatientID int, FirstDateIssued datetime, LastDateIssued
datetime, DaysofTherapy float)
```

```
INSERT INTO #KM (PracticeID, PatientID, FirstDateIssued, LastDateIssued,
DaysofTherapy)
SELECT DISTINCT PracticeID, PatientID, FirstDateIssued, LastDateIssued,
DaysofTherapy
FROM (SELECT DISTINCT KPtable.PracticeID, KPtable.PatientID, FirstDateIssued,
LastDateIssued, DaysofTherapy, COPD = CASE WHEN Diagtable.PracticeID > 0 THEN
1 END
FROM (SELECT DISTINCT PracticeID, PatientID, FirstDateIssued, LastDateIssued,
DATEDIFF(day, FirstDateIssued, LastDateIssued) AS DaysofTherapy
FROM (SELECT DISTINCT PracticeID, PatientID, FirstDateIssued,
MIN(EndofLastDate) AS LastDateIssued
FROM (SELECT derivedtbl_1.PracticeID, derivedtbl_1.PatientID,
derivedtbl_3.FirstDateIssued, derivedtbl_1.EndofLastDate
FROM (SELECT PracticeID, PatientID, DATEADD(day, PrescriptionInterval,
LastDateIssued) AS EndofLastDate
FROM (SELECT derivedtbl_1_1.PracticeID, derivedtbl_1_1.PatientID,
derivedtbl_1_1.LastDateIssued, derivedtbl_2.PrescriptionInterval
FROM (SELECT PracticeID, PatientID, DateIssued AS LastDateIssued
FROM (SELECT PracticeID, PatientID, AgeOnPrescription, DateIssued,
DATEDIFF(DAY, PreviousDateIssuedClass, DateIssued) AS DaysSinceLast,
PrescriptionInterval,
DATEDIFF(day, DateIssued, NextDateIssuedClass) AS DaysToNext,
PrescriptionInterval - DATEDIFF(day, DateIssued, NextDateIssuedClass) AS
Overlap, DrugName, Preparation, rownumberclass
FROM (SELECT PracticeID, PatientID, PrescriptionID, AgeOnPrescription,
DateIssued, PreviousDateIssuedClass, NextDateIssuedClass, DrugName,
Preparation, Dose, Frequency, Quantity,
PrescriptionInterval, DosesPerInhaler, McgPerDayAdj, rownumberclass
FROM tbl_asthma_prescriptions_3_stepdate
WHERE (YEAR(DateIssued) = '2008' OR YEAR(DateIssued) = '2009') AND
(DrugName = 'Beclometasone' OR DrugName = 'Budesonide' OR DrugName LIKE
'Clenil%' OR DrugName LIKE 'Fluticasone%' OR DrugName LIKE 'Qvar%')) AS
table1) AS table2
WHERE (DaysToNext IS NULL)) AS derivedtbl_1_1 LEFT OUTER JOIN
(SELECT DISTINCT PracticeID, PatientID, PrescriptionInterval, DateIssued
FROM tbl_asthma_prescriptions_3_stepdate AS
tbl_asthma_prescriptions_3_stepdate_1) AS derivedtbl_2 ON
derivedtbl_1_1.PracticeID = derivedtbl_2.PracticeID AND
derivedtbl_1_1.PatientID = derivedtbl_2.PatientID AND
derivedtbl_1_1.LastDateIssued = derivedtbl_2.DateIssued) AS table4) AS
derivedtbl_1 INNER JOIN
(SELECT DISTINCT PracticeID, PatientID, MIN(DateIssued) AS FirstDateIssued
FROM tbl_asthma_prescriptions_3_stepdate AS
tbl_asthma_prescriptions_3_stepdate_2
WHERE (YEAR(DateIssued) = '2008' OR YEAR(DateIssued) = '2009') AND
(DrugName = 'Beclometasone' OR DrugName = 'Budesonide' OR DrugName LIKE
'Clenil%' OR DrugName LIKE 'Fluticasone%' OR DrugName LIKE 'Qvar%')
GROUP BY PracticeID, PatientID) AS derivedtbl_3
ON derivedtbl_1.PracticeID = derivedtbl_3.PracticeID AND
derivedtbl_1.PatientID = derivedtbl_3.PatientID
UNION
SELECT derivedtbl_1.PracticeID, derivedtbl_1.PatientID,
derivedtbl_3.DateIssued AS FirstDateIssued, derivedtbl_1.EndofLastDate
FROM (SELECT PracticeID, PatientID, DATEADD(day, PrescriptionInterval,
FirstDateGap) AS EndofLastDate
FROM (SELECT derivedtbl_1_1.PracticeID, derivedtbl_1_1.PatientID,
derivedtbl_1_1.FirstDateGap, derivedtbl_2.PrescriptionInterval
FROM (SELECT DISTINCT PracticeID, PatientID, MIN(DateIssued) AS FirstDateGap
FROM (SELECT PracticeID, PatientID, DateIssued
FROM (SELECT PracticeID, PatientID, AgeOnPrescription, DateIssued,
DATEDIFF(DAY, PreviousDateIssuedClass, DateIssued) AS DaysSinceLast,
PrescriptionInterval, DATEDIFF(day, DateIssued, NextDateIssuedClass) AS
DaysToNext, PrescriptionInterval - DATEDIFF(day, DateIssued,
NextDateIssuedClass) AS Overlap, DrugName, Preparation, rownumberclass
FROM (SELECT PracticeID, PatientID, PrescriptionID, AgeOnPrescription,
DateIssued, PreviousDateIssuedClass, NextDateIssuedClass, DrugName,
Preparation, Dose, Frequency, Quantity, PrescriptionInterval, DosesPerInhaler,
McgPerDayAdj, rownumberclass
FROM tbl_asthma_prescriptions_3_stepdate
WHERE (YEAR(DateIssued) = '2008' OR YEAR(DateIssued) = '2009') AND
(DrugName = 'Beclometasone' OR DrugName = 'Budesonide' OR DrugName LIKE
'Clenil%' OR DrugName LIKE 'Fluticasone%' OR DrugName LIKE 'Qvar%')) AS
table1) AS table2
WHERE (Overlap < - 30)) AS table3
```

```
GROUP BY PracticeID, PatientID) AS derivedtbl_1_1 LEFT OUTER JOIN
(SELECT DISTINCT PracticeID, PatientID, PrescriptionInterval, DateIssued
FROM tbl_asthma_prescriptions_3_stepdate AS
tbl_asthma_prescriptions_3_stepdate_1) AS derivedtbl_2 ON
derivedtbl_1_1.PracticeID = derivedtbl_2.PracticeID AND
derivedtbl_1_1.PatientID = derivedtbl_2.PatientID AND
derivedtbl_1_1.FirstDateGap = derivedtbl_2.DateIssued) AS table4) AS
derivedtbl_1 INNER JOIN (SELECT DISTINCT PracticeID, PatientID,
MIN(DateIssued) AS DateIssued
FROM tbl_asthma_prescriptions_3_stepdate AS
tbl_asthma_prescriptions_3_stepdate_2
WHERE (YEAR(DateIssued) = '2008' OR YEAR(DateIssued) = '2009') AND
(DrugName = 'Beclometasone' OR DrugName = 'Budesonide' OR DrugName LIKE
'Clenil%' OR DrugName LIKE 'Fluticasone%' OR DrugName LIKE 'Qvar%')
GROUP BY PracticeID, PatientID) AS derivedtbl_3 ON derivedtbl_1.PracticeID =
derivedtbl_3.PracticeID AND derivedtbl_1.PatientID = derivedtbl_3.PatientID )
AS table6
GROUP BY PracticeID, PatientID, FirstDateIssued) AS table7) AS KPtable LEFT
JOIN
(SELECT DISTINCT tbl_practice_imports.PracticeID, tbl_copd_data.PatientID
FROM tbl_copd_data INNER JOIN tbl_practice_imports ON tbl_copd_data.importid =
tbl_practice_imports.ID) AS Diagtable
ON KPtable.PracticeID = Diagtable.PracticeID AND KPtable.PatientID =
Diagtable.PatientID) AS Totaltable
WHERE COPD IS NULL AND DaysOfTherapy > '7' AND FirstDateIssued <= '01-01-2009
00:00:00'
SELECT DISTINCT table2.PracticeID, table2.PatientID, Sex, (2007-DOB) AS Age,
DaysofTherapy, RowNumberClass
FROM (SELECT DISTINCT table8.PracticeID, table8.PatientID, FirstDateIssued,
LastDateIssued, DaysofTherapy, RowNumberClass
FROM (SELECT PracticeID, PatientID, FirstDateIssued, LastDateIssued,
DaysofTherapy
FROM #KM) AS table8 LEFT JOIN (SELECT DISTINCT PracticeID, PatientID,
DateIssued, RowNumberClass
FROM tbl_asthma_prescriptions_3_stepdate
WHERE (DrugName = 'Beclometasone' OR DrugName = 'Budesonide' OR DrugName LIKE
'Clenil%' OR DrugName LIKE 'Fluticasone%' OR DrugName LIKE 'Qvar%')) AS table9
ON table8.PracticeID = table9.PracticeID AND table8.PatientID =
table9.PatientID AND table8.FirstDateIssued = table9.DateIssued) AS table2
LEFT JOIN (SELECT DISTINCT PracticeID, PatientID, Sex, AVG(DOB) AS DOB
FROM (SELECT DISTINCT tbl_practice_imports.PracticeID,
tbl_asthma_data.PatientID, tbl_asthma_data.Sex, tbl_asthma_data.AgeInYears,
tbl_practice_imports.ExportDate, YEAR(tbl_practice_imports.ExportDate) -
tbl_asthma_data.AgeInYears AS DOB
FROM tbl_asthma_data INNER JOIN tbl_practice_imports
ON tbl_asthma_data.importid = tbl_practice_imports.ID) AS derivedtbl_1_1
GROUP BY PracticeID, PatientID, Sex) AS table3
ON table2.PracticeID = table3.PracticeID AND table2.PatientID =
table3.PatientID
ORDER BY table2.PracticeID, table2.PatientID
DROP TABLE #KM
```

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```
SELECT DISTINCT PATID, Age, GDR_CD, FirstDateIssued, LastDateIssued,
DATEDIFF(day, FirstDateIssued, LastDateIssued) AS DaysofTherapy
FROM (SELECT DISTINCT PATID, Age, GDR_CD, Class, FirstDateIssued,
MIN(EndofLastDate) AS LastDateIssued
FROM (SELECT derivedtbl_1.PATID, derivedtbl_1.Age, derivedtbl_1.GDR_CD,
derivedtbl_1.Class, derivedtbl_3.FirstDateIssued, derivedtbl_1.EndofLastDate
FROM (SELECT PATID, Age, GDR_CD, Class, DATEADD(day, DAYS_SUP, LastDateIssued)
AS EndofLastDate
FROM (SELECT derivedtbl_1_1.PATID, derivedtbl_1_1.Age, derivedtbl_1_1.GDR_CD,
derivedtbl_1_1.Class, derivedtbl_1_1.LastDateIssued, derivedtbl_2.DAYS_SUP
FROM (SELECT PATID, Age, GDR_CD, Class, FILL_DT AS LastDateIssued
FROM (SELECT PATID, Class, Age, GDR_CD, FILL_DT, DATEDIFF(DAY,
PreviousDateIssuedClass, FILL_DT) AS DaysSinceLast, DAYS_SUP,
DATEDIFF(day, FILL_DT, NextDateIssuedClass) AS DaysToNext, DAYS_SUP -
DATEDIFF(day, FILL_DT, NextDateIssuedClass) AS Overlap, BRND_NM, STRENGTH,
RowNumberClass
FROM (SELECT Indicator.PATID, Demographics.GDR_CD, (2007 - Demographics.YRDOB)
AS Age, Class, FILL_DT, PreviousDateIssuedClass, NextDateIssuedClass, BRND_NM,
STRENGTH, QUANTITY, DAYS_SUP, DosesPerInhaler, McgPerDay, RowNumberClass
FROM Indicator INNER JOIN Overall ON Indicator.PATID = Overall.PATID
INNER JOIN Demographics ON Demographics.PATID = Overall.PATID
INNER JOIN Prescriptions_clean ON Prescriptions_clean.PATID = Overall.PATID
```

```
WHERE (Indicator.Asthma = 1 AND Indicator.COPD = 0 AND
Indicator.Chronic_bronchitis = 0 AND Indicator.Emphysema = 0)
AND (YEAR(FILL_DT) = '2008' OR YEAR(FILL_DT) = '2009') AND
(BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE 'budes%' OR BRND_NM LIKE 'flovent%'
OR BRND_NM LIKE 'pulmicort%' OR BRND_NM LIKE 'qvar%')) AS table1) AS table2
WHERE (DaysToNext IS NULL)) AS derivedtbl_1_1 LEFT OUTER JOIN
(SELECT DISTINCT PATID, Class, DAYS_SUP, FILL_DT
FROM Prescriptions_clean AS Prescriptions_clean_1) AS derivedtbl_2 ON
derivedtbl_1_1.PATID = derivedtbl_2.PATID AND
derivedtbl_1_1.LastDateIssued = derivedtbl_2.FILL_DT AND derivedtbl_1_1.Class
= derivedtbl_2.Class) AS table4) AS derivedtbl_1 INNER JOIN
(SELECT DISTINCT Indicator.PATID, MIN(FILL_DT) AS FirstDateIssued
FROM Indicator INNER JOIN Overall ON Indicator.PATID = Overall.PATID
INNER JOIN Demographics ON Demographics.PATID = Overall.PATID
INNER JOIN Prescriptions_clean ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1 AND Indicator.COPD = 0 AND
Indicator.Chronic_bronchitis = 0 AND Indicator.Emphysema = 0)
AND (YEAR(FILL_DT) = '2008' OR YEAR(FILL_DT) = '2009') AND
(BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE 'budes%' OR BRND_NM LIKE 'flovent%'
OR BRND_NM LIKE 'pulmicort%' OR BRND_NM LIKE 'qvar%')
GROUP BY Indicator.PATID) AS derivedtbl_3
ON derivedtbl_1.PATID = derivedtbl_3.PATID
UNION
SELECT derivedtbl_1.PATID, derivedtbl_1.Age, derivedtbl_1.GDR_CD,
derivedtbl_1.Class, derivedtbl_3.FILL_DT AS FirstDateIssued,
derivedtbl_1.EndofLastDate
FROM (SELECT PATID, Age, GDR_CD, Class, DATEADD(day, DAYS_SUP, FirstDateGap)
AS EndofLastDate
FROM (SELECT derivedtbl_1_1.PATID, derivedtbl_1_1.GDR_CD, derivedtbl_1_1.Age,
derivedtbl_1_1.Class, derivedtbl_1_1.FirstDateGap, derivedtbl_2.DAYS_SUP
FROM (SELECT DISTINCT PATID, GDR_CD, Age, Class, MIN(FILL_DT) AS FirstDateGap
FROM (SELECT PATID, GDR_CD, Age, Class, FILL_DT
FROM (SELECT PATID, GDR_CD, Age, Class, FILL_DT, DATEDIFF(DAY,
PreviousDateIssuedClass, FILL_DT) AS DaysSinceLast, DAYS_SUP, DATEDIFF(day,
FILL_DT, NextDateIssuedClass) AS DaysToNext, DAYS_SUP - DATEDIFF(day, FILL_DT,
NextDateIssuedClass) AS Overlap, RowNumberClass
FROM (SELECT Indicator.PATID, Demographics.GDR_CD, (2007-Demographics.YRDOB)
AS Age, FILL_DT, PreviousDateIssuedClass, NextDateIssuedClass, BRND_NM,
STRENGTH, QUANTITY, DAYS_SUP, DosesPerInhaler, McgPerDay, RowNumberClass,
Class
FROM Indicator INNER JOIN Overall ON Indicator.PATID = Overall.PATID
INNER JOIN Demographics ON Demographics.PATID = Overall.PATID
INNER JOIN Prescriptions_clean ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1 AND Indicator.COPD = 0 AND
Indicator.Chronic_bronchitis = 0 AND Indicator.Emphysema = 0)
AND (YEAR(FILL_DT) = '2008' OR YEAR(FILL_DT) = '2009') AND
(BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE 'budes%' OR BRND_NM LIKE 'flovent%'
OR BRND_NM LIKE 'pulmicort%' OR BRND_NM LIKE 'qvar%')) AS table1) AS table2
WHERE (Overlap < - 30)) AS table3
GROUP BY PATID, Age, GDR_CD, Class) AS derivedtbl_1_1 LEFT OUTER JOIN
(SELECT DISTINCT PATID, Class, DAYS_SUP, FILL_DT
FROM Prescriptions_clean AS Prescriptions_clean_1) AS derivedtbl_2
ON derivedtbl_1_1.PATID = derivedtbl_2.PATID AND derivedtbl_1_1.FirstDateGap =
derivedtbl_2.FILL_DT AND derivedtbl_1_1.Class = derivedtbl_2.Class) AS table4)
AS derivedtbl_1 INNER JOIN
(SELECT DISTINCT Indicator.PATID, Class, MIN(FILL_DT) AS FILL_DT
FROM Indicator INNER JOIN Overall ON Indicator.PATID = Overall.PATID
INNER JOIN Demographics ON Demographics.PATID = Overall.PATID
INNER JOIN Prescriptions_clean ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1 AND Indicator.COPD = 0 AND
Indicator.Chronic_bronchitis = 0 AND Indicator.Emphysema = 0)
AND (YEAR(FILL_DT) = '2008' OR YEAR(FILL_DT) = '2009')
GROUP BY Indicator.PATID, Class) AS derivedtbl_3
ON derivedtbl_1.PATID = derivedtbl_3.PATID AND derivedtbl_1.Class =
derivedtbl_3.Class) AS table6
GROUP BY PATID, Age, GDR_CD, Class, FirstDateIssued) AS table7
WHERE FirstDateIssued <= '01-01-2009 00:00:00'
ORDER BY DaysofTherapy
```

19

```
SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_2
WHERE (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Salbutamol') AND  (Preparation NOT LIKE '%SOLN%') AND
(Preparation NOT LIKE '%SYRUP%') AND (Preparation NOT LIKE '%TABS%') OR
(YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
```

```
(DrugName = 'Terbutaline') AND  (Preparation NOT LIKE '%SYRUP%') AND
(Preparation NOT LIKE '%TABS%') AND  (Preparation NOT LIKE '%Amp%')
EXCEPT
SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_2
WHERE (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Aminophylline Mr' OR DrugName LIKE 'Bamb%' OR DrugName =
'Beclometasone' OR DrugName = 'Budesonide' OR DrugName = 'Ciclesonide' OR
DrugName LIKE 'Clenil%' OR DrugName = 'Filair' OR DrugName = 'Fluticasone' OR
DrugName = 'Foradil' OR DrugName = 'Formoterol' OR DrugName = 'Fostair 100/6'
OR DrugName = 'Mometasone' OR DrugName LIKE 'Phyllo%' OR DrugName LIKE 'Qvar%'
OR DrugName = 'Salmeterol' OR DrugName LIKE 'Seretide%' OR DrugName LIKE
'Symbicort%' OR DrugName = 'Uniphyllin Continus' OR DrugName = 'Theophylline'
OR DrugName = 'Slophyllin' OR DrugName = 'Ventmax Sr' OR DrugName = 'Volmax')
OR (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName LIKE 'Salbutamol%') AND (Preparation LIKE '%SOLN%') OR
 (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName LIKE 'Salbutamol%') AND (Preparation LIKE '%SYRUP%') OR
 (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName LIKE 'Salbutamol%') AND (Preparation LIKE '%TABS%') OR
 (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Terbutaline') AND (Preparation LIKE '%SYRUP%') OR
 (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Terbutaline') AND (Preparation LIKE '%TABS%') OR
 (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Terbutaline') AND (Preparation LIKE '%Amp%') OR
 (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Prednisolone') AND (Dose NOT LIKE 'as directed%') AND
(Frequency NOT LIKE 'as directed%') AND (Dose NOT LIKE 'as needed%') AND
(Frequency NOT LIKE 'as needed%') AND (PrescriptionInterval > '14') AND
(Frequency NOT LIKE '%titrating%')
```

20

```
(SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_3
WHERE (AgeonPrescription > '12') AND (YEAR(DateIssued) = '2008') AND
(DrugName = 'Beclometasone' AND McgPerDay > '0' AND McgPerDay <= '400' OR
DrugName = 'Budesonide' AND McgPerDay > '0' AND McgPerDay <= '400' OR
DrugName = 'Ciclesonide' AND McgPerDay > '0' AND McgPerDay <= '200' OR
DrugName LIKE 'Clenil%' AND McgPerDay > '0' AND McgPerDay <= '400' OR
DrugName = 'Filair' AND McgPerDay > '0' AND McgPerDay <= '400' OR
DrugName = 'Fluticasone' AND McgPerDay > '0' AND McgPerDay <= '200' OR
DrugName = 'Mometasone' AND McgPerDay > '0' AND McgPerDay <= '200' OR
DrugName LIKE 'Qvar%' AND McgPerDay > '0' AND McgPerDay <= '200')
EXCEPT
SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_3
WHERE (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Aminophylline Mr' OR DrugName LIKE 'Bamb%' OR DrugName =
'Foradil' OR DrugName = 'Formoterol' OR DrugName = 'Fostair 100/6' OR DrugName
LIKE 'Phyllo%' OR DrugName = 'Salmeterol' OR DrugName LIKE 'Seretide%' OR
DrugName LIKE 'Symbicort%' OR DrugName = 'Aminophylline Mr' OR DrugName =
'Uniphyllin Continus' OR DrugName = 'Theophylline' OR DrugName = 'Slophyllin'
OR DrugName = 'Ventmax Sr' OR DrugName = 'Volmax' OR DrugName LIKE
'Salbutamol%' AND Preparation LIKE '%SOLN%' OR DrugName LIKE 'Salbutamol%' AND
Preparation LIKE '%SYRUP%' OR DrugName LIKE 'Salbutamol%' AND Preparation LIKE
'%TABS%' OR DrugName = 'Terbutaline' AND Preparation LIKE '%SYRUP%' OR
DrugName = 'Terbutaline' AND Preparation LIKE '%TABS%' OR DrugName =
'Terbutaline' AND Preparation LIKE '%Amp%' OR DrugName = 'Prednisolone' AND
Dose NOT LIKE 'as directed%' AND Frequency NOT LIKE 'as directed%' AND Dose
NOT LIKE 'as needed%' AND Frequency NOT LIKE 'as needed%' AND
rescriptionInterval > '14' AND Frequency NOT LIKE '%titrating%' OR
DrugName = 'Beclometasone' AND McgPerDay > '400' OR
DrugName = 'Budesonide' AND McgPerDay > '400' OR
DrugName = 'Ciclesonide' AND McgPerDay > '200' OR
DrugName LIKE 'Clenil%' AND McgPerDay > '400' OR
DrugName = 'Filair' AND McgPerDay > '400' OR
DrugName = 'Fluticasone' AND McgPerDay > '200' OR
DrugName = 'Mometasone' AND McgPerDay > '200'  OR
DrugName LIKE 'Qvar%' AND McgPerDay > '200'))
UNION
(SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_3
WHERE (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Aminophylline Mr' OR DrugName LIKE 'Phyllo%' OR DrugName =
'Aminophylline Mr' OR DrugName = 'Uniphyllin Continus' OR DrugName =
'Theophylline' OR DrugName = 'Slophyllin')
EXCEPT
SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_3
```

```
WHERE (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName LIKE 'Bamb%' OR DrugName = 'Foradil' OR DrugName = 'Formoterol' OR
DrugName = 'Fostair 100/6' OR DrugName = 'Salmeterol' OR DrugName LIKE
'Seretide%' OR DrugName LIKE 'Symbicort%' OR DrugName = 'Ventmax Sr' OR
DrugName = 'Volmax' OR DrugName LIKE 'Salbutamol%' AND Preparation LIKE
'%SOLN%' OR DrugName LIKE 'Salbutamol%' AND Preparation LIKE '%SYRUP%' OR
DrugName LIKE 'Salbutamol%' AND Preparation LIKE '%TABS%' OR DrugName =
'Terbutaline' AND Preparation LIKE '%SYRUP%' OR DrugName = 'Terbutaline' AND
Preparation LIKE '%TABS%' OR DrugName = 'Terbutaline' AND Preparation LIKE
'%Amp%' OR DrugName = 'Prednisolone' AND Dose NOT LIKE 'as directed%' AND
Frequency NOT LIKE 'as directed%' AND Dose NOT LIKE 'as needed%' AND Frequency
NOT LIKE 'as needed%' AND PrescriptionInterval > '14' AND Frequency NOT LIKE
'%titrating%' OR DrugName = 'Beclometasone' OR  DrugName = 'Budesonide' OR
DrugName = 'Ciclesonide' OR  DrugName LIKE 'Clenil%' OR DrugName = 'Filair' OR
DrugName = 'Fluticasone' OR DrugName = 'Mometasone' OR DrugName LIKE 'Qvar%'))
```

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```
SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_3
WHERE (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Fostair 100/6' AND McgPerDay > '0' AND McgPerDay <= '400' OR
DrugName LIKE 'Seretide%' AND McgPerDay > '0' AND McgPerDay <= '400' OR
DrugName LIKE 'Symbicort%' AND McgPerDay > '0' AND McgPerDay <= '800' OR
DrugName = 'Foradil' OR DrugName = 'Formoterol' OR DrugName = 'Salmeterol' OR
DrugName = 'Beclometasone' AND McgPerDay > '400' AND McgPerDay <= '800' OR
DrugName = 'Budesonide' AND McgPerDay > '400' AND McgPerDay <= '800' OR
DrugName = 'Ciclesonide' AND McgPerDay > '200' AND McgPerDay <= '400' OR
DrugName LIKE 'Clenil%' AND McgPerDay > '400' AND McgPerDay <= '800' OR
DrugName = 'Filair' AND McgPerDay > '400' AND McgPerDay <= '800' OR
DrugName = 'Fluticasone' AND McgPerDay > '200' AND McgPerDay <= '400' OR
DrugName = 'Mometasone' AND McgPerDay > '200' AND McgPerDay <= '400' OR
DrugName LIKE 'Qvar%' AND McgPerDay > '200' AND McgPerDay <= '400')
EXCEPT
SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_3
WHERE (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Aminophylline Mr' OR DrugName LIKE 'Bamb%' OR DrugName =
'Phyllocontin Continus' OR DrugName LIKE 'Phyllocontin%' OR DrugName =
'Aminophylline Mr' OR DrugName = 'Uniphyllin Continus' OR DrugName =
'Theophylline' OR DrugName = 'Slophyllin' OR DrugName = 'Ventmax Sr' OR
DrugName = 'Volmax' OR
DrugName = 'Fostair 100/6' AND McgPerDay > '400' OR
DrugName LIKE 'Seretide%' AND McgPerDay > '400' OR
DrugName LIKE 'Symbicort%' AND McgPerDay > '800' OR
(DrugName = 'Salbutamol' AND Preparation LIKE '%SOLN%') OR
(DrugName = 'Salbutamol' AND Preparation LIKE '%SYRUP%') OR
(DrugName = 'Salbutamol' AND Preparation LIKE '%TABS%') OR
(DrugName = 'Terbutaline' AND Preparation LIKE '%SYRUP%') OR
(DrugName = 'Terbutaline' AND Preparation LIKE '%TABS%') OR
(DrugName = 'Terbutaline' AND Preparation LIKE '%Amp%') OR
(DrugName = 'Prednisolone' AND (Dose NOT LIKE 'as directed%' AND Frequency NOT
LIKE 'as directed%' AND Dose NOT LIKE 'as needed%' AND Frequency NOT LIKE 'as
needed%' AND PrescriptionInterval > '14' AND Frequency NOT LIKE
'%titrating%')) OR
DrugName = 'Beclometasone' AND McgPerDay > '800' OR
DrugName = 'Budesonide' AND McgPerDay > '800' OR
DrugName = 'Ciclesonide' AND McgPerDay > '400' OR
DrugName LIKE 'Clenil%' AND McgPerDay > '800' OR
DrugName = 'Filair' AND McgPerDay > '800' OR
DrugName = 'Fluticasone' AND McgPerDay > '400' OR
DrugName = 'Mometasone' AND McgPerDay > '400' OR
DrugName LIKE 'Qvar%' AND McgPerDay > '400')
```

22

```
SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_3
WHERE (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Fostair 100/6' AND McgPerDay > '400' OR
DrugName LIKE 'Seretide%' AND McgPerDay > '400' OR
DrugName LIKE 'Symbicort%' AND McgPerDay > '800' OR
DrugName = 'Beclometasone' AND McgPerDay > '800' OR
DrugName = 'Budesonide' AND McgPerDay > '800' OR
DrugName = 'Ciclesonide' AND McgPerDay > '400' OR
DrugName LIKE 'Clenil%' AND McgPerDay > '800' OR
DrugName = 'Filair' AND McgPerDay > '800' OR
DrugName = 'Fluticasone' AND McgPerDay > '400' OR
DrugName = 'Mometasone' AND McgPerDay > '400' OR
DrugName LIKE 'Qvar%' AND McgPerDay > '400')
EXCEPT
```

```
SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_2
WHERE (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Prednisolone') AND (Dose NOT LIKE 'as directed%') AND
 (Frequency NOT LIKE 'as directed%') AND (Dose NOT LIKE 'as needed%') AND
(Frequency NOT LIKE 'as needed%') AND (PrescriptionInterval > '14') AND
(Frequency NOT LIKE '%titrating%')
```

23

```
SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_2
WHERE (YEAR(DateIssued) = '2008') AND (AgeOnPrescription > '12') AND
(DrugName = 'Prednisolone') AND (Dose NOT LIKE 'as directed%') AND
(Frequency NOT LIKE 'as directed%') AND (Dose NOT LIKE 'as needed%') AND
(Frequency NOT LIKE 'as needed%') AND (PrescriptionInterval > '14') AND
(Frequency NOT LIKE '%titrating%')
INTERSECT
(SELECT DISTINCT PracticeID, PatientID FROM tbl_asthma_prescriptions_3
WHERE (AgeonPrescription > '12') AND (YEAR(DateIssued) = '2008') AND
(DrugName = 'Aminophylline Mr' OR  DrugName LIKE 'Bamb%' OR
(DrugName = 'Beclometasone' AND Preparation LIKE '%/dose%' AND McgPerDay <>
'0')  OR DrugName = 'Budesonide' AND McgPerDay <> '0' OR DrugName =
'Ciclesonide'AND McgPerDay <> '0' OR (DrugName LIKE 'Clenil%' AND Preparation
LIKE '%/dose%' AND McgPerDay <> '0') OR (DrugName = 'Filair' AND McgPerDay <>
'0') OR (DrugName = 'Fluticasone' AND McgPerDay <> '0') OR (DrugName =
'Foradil' AND McgPerDay <> '0') OR DrugName = 'Formoterol' OR
(DrugName = 'Fostair 100/6' AND McgPerDay <> '0') OR (DrugName = 'Mometasone'
AND McgPerDay <> '0') OR DrugName LIKE 'Phyllo%' OR (DrugName LIKE 'Qvar%' AND
McgPerDay <> '0') OR DrugName = 'Salmeterol' OR DrugName LIKE 'Salbutamol%' OR
(DrugName LIKE 'Seretide%' AND McgPerDay <> '0') OR (DrugName LIKE
'Symbicort%' AND McgPerDay <> '0') OR DrugName = 'Uniphyllin Continus' OR
DrugName = 'Terbutaline' OR  DrugName = 'Theophylline' OR  DrugName =
'Slophyllin' OR DrugName = 'Ventmax Sr' OR DrugName = 'Volmax'))
```

24

```
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
(BRND_NM LIKE 'accuneb' OR (BRND_NM LIKE 'Albuterol%' AND (STRENGTH NOT LIKE
'2MG%' OR STRENGTH NOT LIKE '4MG%' OR STRENGTH NOT LIKE '5MG%' OR STRENGTH <>
'8MG')) OR BRND_NM LIKE 'maxair%' OR BRND_NM LIKE 'proair%' OR BRND_NM LIKE
'ventolin%' OR BRND_NM LIKE 'xopenex%')
EXCEPT
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'Albuterol%' AND (STRENGTH LIKE '2MG%' OR STRENGTH = '4MG' OR
STRENGTH LIKE '5MG%' OR STRENGTH = '8MG')) OR BRND_NM LIKE 'terbutaline%' OR
BRND_NM LIKE 'vospire%' OR BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%'
OR BRND_NM LIKE 'azmacort%' OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE
'pulmicort flexhaler%' OR BRND_NM LIKE 'pulmicort  %' OR BRND_NM LIKE
'budesonide%' OR BRND_NM LIKE 'qvar%' OR BRND_NM LIKE 'advair%' OR BRND_NM
LIKE 'symbicort%' OR BRND_NM LIKE 'brovana%' OR BRND_NM LIKE 'foradil%' OR
BRND_NM LIKE 'perforomist%' OR BRND_NM LIKE 'serevent%' OR BRND_NM LIKE
'elixophyllin%' OR BRND_NM LIKE 'theo%' OR BRND_NM LIKE 'accolate%' OR BRND_NM
LIKE 'singulair%' OR BRND_NM LIKE 'zyflo%' OR BRND_NM LIKE 'tilade%' OR
(BRND_NM LIKE 'methylpred%' AND DAYS_SUP > '14') OR
(BRND_NM LIKE 'prednisone%' AND DAYS_SUP > '14'))
```

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```
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'aerobid%' AND McgPerDay > '0' AND McgPerDay <= '1000')  OR
(BRND_NM LIKE 'asmanex%' AND McgPerDay > '0' AND McgPerDay <= '200') OR
(BRND_NM LIKE 'azmacort%' AND McgPerDay > '0' AND McgPerDay <= '1000') OR
(BRND_NM LIKE 'flovent%' AND McgPerDay > '0' AND McgPerDay <= '200') OR
```

```
 (BRND_NM LIKE 'pulmicort fle%'AND  McgPerDay > '0' AND McgPerDay <= '400') OR
(BRND_NM LIKE 'budesonide%' AND  McgPerDay > '0' AND McgPerDay <= '1000') OR
(BRND_NM LIKE 'pulmicort  %' AND  McgPerDay > '0' AND McgPerDay <= '1000') OR
(BRND_NM LIKE 'qvar%'AND  McgPerDay > '0' AND McgPerDay <= '160'))
EXCEPT
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'Albuterol%' AND (STRENGTH LIKE '2MG%' OR STRENGTH = '4MG' OR
STRENGTH LIKE '5MG%' OR STRENGTH = '8MG')) OR BRND_NM LIKE 'terbutaline%' OR
BRND_NM LIKE 'vospire%' OR
(BRND_NM LIKE 'aerobid%' AND McgPerDay > '1000') OR
(BRND_NM LIKE 'asmanex%' AND McgPerDay > '200')   OR
(BRND_NM LIKE 'azmacort%' AND McgPerDay > '1000') OR
(BRND_NM LIKE 'flovent%' AND McgPerDay > '200')  OR
(BRND_NM LIKE 'pulmicort flexhaler%' AND McgPerDay > '400')  OR
(BRND_NM LIKE 'budesonide%' AND McgPerDay > '1000')  OR
(BRND_NM LIKE 'pulmicort  %' AND McgPerDay > '1000')  OR
(BRND_NM LIKE 'qvar%' AND McgPerDay > '160')  OR
BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%' OR BRND_NM LIKE 'brovana%'
OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE 'perforomist%' OR BRND_NM LIKE
'serevent%' OR BRND_NM LIKE 'elixophyllin%' OR BRND_NM LIKE 'theo%' OR
BRND_NM LIKE 'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM LIKE 'zyflo%'
OR BRND_NM LIKE 'tilade%' OR
(BRND_NM LIKE 'methylpred%' AND DAYS_SUP > '14') OR
(BRND_NM LIKE 'prednisone%' AND DAYS_SUP > '14')))
UNION
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
(BRND_NM LIKE 'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM LIKE
'zyflo%' OR BRND_NM LIKE 'tilade%' OR BRND_NM LIKE 'theo%' OR BRND_NM LIKE
'elixophyllin%' OR (BRND_NM LIKE 'Albuterol%' AND (STRENGTH LIKE '2MG%' OR
STRENGTH = '4MG' OR STRENGTH LIKE '5MG%' OR STRENGTH = '8MG')) OR BRND_NM LIKE
'terbutaline%' OR BRND_NM LIKE 'vospire%')
EXCEPT
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
(BRND_NM LIKE 'aerobid%'  OR BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE
'azmacort%'  OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE 'pulmicort flexhaler%'
OR BRND_NM LIKE 'pulmicort  %' OR BRND_NM LIKE 'budesonide%' OR BRND_NM LIKE
'qvar%' OR BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%' OR BRND_NM LIKE
'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE 'perforomist%' OR
BRND_NM LIKE 'serevent%' OR
(BRND_NM LIKE 'methylpred%' AND DAYS_SUP > '14') OR
(BRND_NM LIKE 'prednisone%' AND DAYS_SUP > '14')))
```

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```
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'advair%' AND McgPerDay > '0' AND McgPerDay <= '400') OR
 (BRND_NM LIKE 'symbicort%' AND  McgPerDay > '0' AND McgPerDay <= '800') OR
BRND_NM LIKE 'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE
'perforomist%' OR BRND_NM LIKE 'serevent%' OR
(BRND_NM LIKE 'aerobid%' AND McgPerDay > '1000' AND McgPerDay <= '2000') OR
(BRND_NM LIKE 'asmanex%' AND McgPerDay > '200' AND McgPerDay <= '400')   OR
(BRND_NM LIKE 'azmacort%' AND McgPerDay > '1000' AND McgPerDay <= '2000') OR
```

```
(BRND_NM LIKE 'flovent%' AND McgPerDay > '200' AND McgPerDay <= '400')  OR
 (BRND_NM LIKE 'pulmicort f%' AND McgPerDay > '400' AND McgPerDay <= '800') OR
(BRND_NM LIKE 'budeso%' AND McgPerDay > '1000' AND McgPerDay <= '2000') OR
(BRND_NM LIKE 'pulmicort  %' AND McgPerDay > '1000' AND McgPerDay <= '2000')
OR
(BRND_NM LIKE 'qvar%' AND McgPerDay > '160' AND McgPerDay <= '320'))
EXCEPT
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'Albuterol%' AND (STRENGTH LIKE '2MG%' OR STRENGTH = '4MG' OR
STRENGTH LIKE '5MG%' OR STRENGTH = '8MG')) OR BRND_NM LIKE 'terbutaline%' OR
BRND_NM LIKE 'vospire%' OR
(BRND_NM LIKE 'aerobid%' AND McgPerDay > '2000') OR
(BRND_NM LIKE 'asmanex%' AND McgPerDay > '400')   OR
(BRND_NM LIKE 'azmacort%' AND McgPerDay > '2000') OR
(BRND_NM LIKE 'flovent%' AND McgPerDay > '400')  OR
 (BRND_NM LIKE 'pulmicort flexhaler%' AND McgPerDay > '800')  OR
(BRND_NM LIKE 'budesonide%' AND McgPerDay > '2000')  OR
(BRND_NM LIKE 'pulmicort  %' AND McgPerDay > '2000')  OR
(BRND_NM LIKE 'qvar%' AND McgPerDay > '320')  OR
(BRND_NM LIKE 'advair%' AND McgPerDay > '400')  OR
(BRND_NM LIKE 'symbicort%' AND McgPerDay > '800')  OR
BRND_NM LIKE 'elixophyllin%' OR BRND_NM LIKE 'theo%' OR BRND_NM LIKE
'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM LIKE 'zyflo%' OR BRND_NM
LIKE 'tilade%' OR
(BRND_NM LIKE 'methylpred%' AND DAYS_SUP > '14') OR
(BRND_NM LIKE 'prednisone%' AND DAYS_SUP > '14')))
UNION
(SELECT DISTINCT d1.PATID
FROM (SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'aerobid%' AND McgPerDay > '0' AND McgPerDay <= '2000') OR
(BRND_NM LIKE 'asmanex%' AND McgPerDay > '0' AND McgPerDay <= '400')   OR
(BRND_NM LIKE 'azmacort%' AND McgPerDay > '0' AND McgPerDay <= '2000') OR
(BRND_NM LIKE 'flovent%' AND McgPerDay > '0' AND McgPerDay <= '400')  OR
 (BRND_NM LIKE 'pulmicort fle%' AND McgPerDay > '0' AND McgPerDay <= '800') OR
(BRND_NM LIKE 'budesonide%' AND McgPerDay > '0' AND McgPerDay <= '2000')  OR
(BRND_NM LIKE 'pulmicort  %' AND McgPerDay > '0' AND McgPerDay <= '2000')  OR
(BRND_NM LIKE 'qvar%' AND McgPerDay > '0' AND McgPerDay <= '320'))) as d1
INNER JOIN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'Albuterol%' AND (STRENGTH LIKE '2MG%' OR STRENGTH = '4MG' OR
STRENGTH LIKE '5MG%' OR STRENGTH = '8MG')) OR BRND_NM LIKE 'terbutaline%' OR
BRND_NM LIKE 'vospire%' OR BRND_NM LIKE 'elixophyllin%' OR BRND_NM LIKE
'theo%' OR BRND_NM LIKE 'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM
LIKE 'zyflo%' OR BRND_NM LIKE 'tilade%')) as d2
ON d1.PATID = d2.PATID
EXCEPT
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'aerobid%' AND McgPerDay > '2000') OR
(BRND_NM LIKE 'asmanex%' AND McgPerDay > '400')   OR
(BRND_NM LIKE 'azmacort%' AND McgPerDay > '2000') OR
```

```
(BRND_NM LIKE 'flovent%' AND McgPerDay > '400')  OR
(BRND_NM LIKE 'pulmicort flexhaler%' AND McgPerDay > '800')  OR
(BRND_NM LIKE 'budesonide%' AND McgPerDay > '2000')  OR
(BRND_NM LIKE 'pulmicort  %' AND McgPerDay > '2000')  OR
(BRND_NM LIKE 'qvar%' AND McgPerDay > '320')  OR
(BRND_NM LIKE 'advair%')  OR (BRND_NM LIKE 'symbicort%') OR BRND_NM LIKE
'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE 'perforomist%' OR
BRND_NM LIKE 'serevent%' OR (BRND_NM LIKE 'methylpred%' AND DAYS_SUP > '14')
OR (BRND_NM LIKE 'prednisone%' AND DAYS_SUP > '14')))
```

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```
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'advair%' AND McgPerDay > '400')  OR
 (BRND_NM LIKE 'symbicort%' AND McgPerDay > '800') OR
(BRND_NM LIKE 'aerobid%' AND McgPerDay > '2000') OR
(BRND_NM LIKE 'asmanex%' AND McgPerDay > '400' )   OR
(BRND_NM LIKE 'azmacort%' AND McgPerDay > '2000') OR
(BRND_NM LIKE 'flovent%' AND McgPerDay > '400')  OR
(BRND_NM LIKE 'pulmicort fle%' AND McgPerDay > '800')  OR
(BRND_NM LIKE 'budesonide%' AND McgPerDay > '2000')  OR
(BRND_NM LIKE 'pulmicort  %' AND McgPerDay > '2000')  OR
(BRND_NM LIKE 'qvar%' AND McgPerDay > '320'))
EXCEPT
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'methylpred%' AND DAYS_SUP > '14') OR
(BRND_NM LIKE 'prednisone%' AND DAYS_SUP > '14')))
UNION
(SELECT DISTINCT d3.PATID
FROM (SELECT DISTINCT d1.PATID
FROM (SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'aerobid%' AND McgPerDay > '2000') OR
(BRND_NM LIKE 'asmanex%' AND McgPerDay > '400' )   OR
(BRND_NM LIKE 'azmacort%' AND McgPerDay > '2000') OR
(BRND_NM LIKE 'flovent%' AND McgPerDay > '400')  OR
(BRND_NM LIKE 'pulmicort flexhaler%' AND McgPerDay > '800')  OR
(BRND_NM LIKE 'budesonide%' AND McgPerDay > '2000')  OR
(BRND_NM LIKE 'pulmicort  %' AND McgPerDay > '2000')  OR
(BRND_NM LIKE 'qvar%' AND McgPerDay > '320'))
EXCEPT
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'Albuterol%' AND (STRENGTH LIKE '2MG%' OR STRENGTH = '4MG' OR
STRENGTH LIKE '5MG%' OR STRENGTH = '8MG')) OR BRND_NM LIKE 'terbutaline%' OR
BRND_NM LIKE 'vospire%' OR BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%'
OR BRND_NM LIKE 'elixophyllin%' OR BRND_NM LIKE 'theo%' OR BRND_NM LIKE
'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM LIKE 'zyflo%' OR BRND_NM
LIKE 'tilade%' OR BRND_NM LIKE 'brovana%' OR BRND_NM LIKE 'foradil%' OR
BRND_NM LIKE 'perforomist%' OR BRND_NM LIKE 'serevent%' OR
(BRND_NM LIKE 'methylpred%' AND DAYS_SUP > '14') OR
(BRND_NM LIKE 'prednisone%' AND DAYS_SUP > '14')))
UNION
(SELECT DISTINCT d1.PATID
```

```
FROM (SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'aerobid%' AND McgPerDay > '2000') OR
(BRND_NM LIKE 'asmanex%' AND McgPerDay > '400')   OR
(BRND_NM LIKE 'azmacort%' AND McgPerDay > '2000') OR
(BRND_NM LIKE 'flovent%' AND McgPerDay > '400')  OR
(BRND_NM LIKE 'pulmicort flexhaler%' AND McgPerDay > '800')  OR
(BRND_NM LIKE 'budesonide%' AND McgPerDay > '2000')  OR
(BRND_NM LIKE 'pulmicort  %' AND McgPerDay > '2000')  OR
(BRND_NM LIKE 'qvar%' AND McgPerDay > '320') OR
BRND_NM LIKE 'advair%' AND McgPerDay > '400' OR
BRND_NM LIKE 'symbicort%' AND McgPerDay > '800')) as d1 INNER JOIN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'Albuterol%' AND (STRENGTH LIKE '2MG%' OR STRENGTH = '4MG' OR
STRENGTH LIKE '5MG%' OR STRENGTH = '8MG')) OR BRND_NM LIKE 'terbutaline%' OR
BRND_NM LIKE 'vospire%' OR BRND_NM LIKE 'elixophyllin%' OR BRND_NM LIKE
'theo%' OR BRND_NM LIKE 'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM
LIKE 'zyflo%' OR BRND_NM LIKE 'tilade%')) as d2
ON d1.PATID = d2.PATID
EXCEPT
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'methylpred%' AND DAYS_SUP > '14') OR
(BRND_NM LIKE 'prednisone%' AND DAYS_SUP > '14')))
```

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```
SELECT DISTINCT d1.PATID
FROM(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
((BRND_NM LIKE 'methylpred%' AND DAYS_SUP > '14') OR
(BRND_NM LIKE 'prednisone%' AND DAYS_SUP > '14'))) AS d1 INNER JOIN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Asthma = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) =
'2008' AND (2008 - Overall.YRDOB) > 12 AND
(BRND_NM LIKE 'Accuneb%' OR BRND_NM LIKE 'Albuterol%' OR BRND_NM LIKE
'maxair%' OR BRND_NM LIKE 'proair%' OR BRND_NM LIKE 'terbutaline%' OR BRND_NM
LIKE 'ventolin%' OR BRND_NM LIKE 'vospire%' OR BRND_NM LIKE 'xopenex%' OR
BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE 'azmacort%'
OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE 'pulmicort flexhaler%' OR BRND_NM
LIKE 'budesonide%' OR BRND_NM LIKE 'pulmicort  %' OR BRND_NM LIKE 'qvar%' OR
BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%' OR BRND_NM LIKE 'brovana%'
OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE 'perforomist%' OR BRND_NM LIKE
'serevent%' OR BRND_NM LIKE 'elixophyllin%' OR BRND_NM LIKE 'theo%' OR BRND_NM
LIKE 'accolate%' OR BRND_NM LIKE 'singulair%' OR BRND_NM LIKE 'zyflo%' OR
BRND_NM LIKE 'tilade%')) AS d2
ON d1.PATID = d2.PATID
```

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```
CREATE TABLE #ICS
(PracticeID int, PatientID int, IndexDate datetime)
INSERT INTO #ICS (PracticeID, PatientID, IndexDate)
SELECT DISTINCT table1.PracticeID, table1.PatientID, MIN(DateIssued) AS
IndexDate
FROM ((SELECT DISTINCT PracticeID, PatientID
FROM tbl_asthma_prescriptions_3_stepdate
WHERE (DrugName LIKE 'seretide%' OR DrugName LIKE 'symbi%') AND
YEAR(DateIssued) = '2008' AND DateRank = 1
INTERSECT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_asthma_prescriptions_3_stepdate
WHERE YEAR(DateIssued) = '2007' AND MONTH(DateIssued) < '6')
EXCEPT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_asthma_prescriptions_3_stepdate
WHERE (DrugName LIKE 'seretide%' OR DrugName LIKE 'symbi%') AND
YEAR(DateIssued) < '2008') AS table1 LEFT JOIN
tbl_asthma_prescriptions_3_stepdate
ON table1.PracticeID = tbl_asthma_prescriptions_3_stepdate.PracticeID AND
table1.PatientID = tbl_asthma_prescriptions_3_stepdate.PatientID
WHERE (DrugName LIKE 'seretide%' OR DrugName LIKE 'symbi%') AND
YEAR(DateIssued) = '2008' AND DateRank = 1
GROUP BY table1.PracticeID, table1.PatientID
UNION
SELECT DISTINCT table1.PracticeID, table1.PatientID, MIN(DateIssued) AS
IndexDate
FROM ((SELECT DISTINCT PracticeID, PatientID
FROM tbl_asthma_prescriptions_3_stepdate
WHERE (DrugName LIKE 'seretide%' OR DrugName LIKE 'symbi%') AND
YEAR(DateIssued) = '2009' AND DateRank = 1
INTERSECT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_asthma_prescriptions_3_stepdate
WHERE YEAR(DateIssued) = '2008' AND MONTH(DateIssued) < '6')
EXCEPT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_asthma_prescriptions_3_stepdate
WHERE (DrugName LIKE 'seretide%' OR DrugName LIKE 'symbi%') AND
YEAR(DateIssued) < '2009') AS table1 LEFT JOIN
tbl_asthma_prescriptions_3_stepdate
ON table1.PracticeID = tbl_asthma_prescriptions_3_stepdate.PracticeID AND
table1.PatientID = tbl_asthma_prescriptions_3_stepdate.PatientID
WHERE (DrugName LIKE 'seretide%' OR DrugName LIKE 'symbi%') AND
YEAR(DateIssued) = '2009' AND DateRank = 1
GROUP BY table1.PracticeID, table1.PatientID
SELECT DISTINCT #ICS.PracticeID, #ICS.PatientID, MAX(Dose)
FROM #ICS LEFT JOIN
(SELECT DISTINCT #ICS.PracticeID, #ICS.PatientID, #ICS.IndexDate, Dose = CASE
WHEN McgPerDayAdj IS NOT NULL THEN McgPerDayAdj
WHEN McgPerDayAdj IS NULL THEN 0 END
FROM #ICS LEFT JOIN tbl_asthma_prescriptions_3_stepdate
ON #ICS.PracticeID = tbl_asthma_prescriptions_3_stepdate.PracticeID AND
#ICS.PatientID = tbl_asthma_prescriptions_3_stepdate.PatientID
WHERE DATEDIFF(DAY, DateIssued, IndexDate) < 365 AND DATEDIFF(DAY, DateIssued,
IndexDate) >= 0 AND (DrugName LIKE 'beclo%' OR DrugName LIKE 'budes%' OR
DrugName LIKE 'clenil%' OR DrugName LIKE 'flutica%' OR DrugName LIKE 'qvar%'
OR DrugName LIKE 'mometa%' OR DrugName LIKE 'filair%' OR DrugName LIKE
'cicles%')) AS table2
ON #ICS.PracticeID = table2.PracticeID AND
#ICS.PatientID = table2.PatientID
GROUP BY #ICS.PracticeID, #ICS.PatientID
ORDER BY #ICS.PracticeID, #ICS.PatientID
DROP TABLE #ICS
```

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```
CREATE TABLE #ICS
(PATID int, IndexDate datetime)
INSERT INTO #ICS (PATID, IndexDate)
SELECT DISTINCT table1.PATID, MIN(FILL_DT) AS IndexDate
FROM ((SELECT DISTINCT Prescriptions_clean.PATID
FROM Prescriptions_clean INNER JOIN Indicator
ON Prescriptions_clean.PATID = Indicator.PATID
WHERE (BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbi%') AND YEAR(FILL_DT) =
'2008' AND RowNumber = 1 AND Indicator.Asthma = 1
```

```
INTERSECT
SELECT DISTINCT Prescriptions_clean.PATID
FROM Prescriptions_clean INNER JOIN Indicator
ON Prescriptions_clean.PATID = Indicator.PATID
WHERE YEAR(FILL_DT) = '2007' AND
MONTH(FILL_DT) < '6' AND Indicator.Asthma = 1)
EXCEPT
SELECT DISTINCT Prescriptions_clean.PATID
FROM Prescriptions_clean INNER JOIN Indicator
ON Prescriptions_clean.PATID = Indicator.PATID
WHERE (BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbi%') AND YEAR(FILL_DT) <
'2008' AND Indicator.Asthma = 1) AS table1 LEFT JOIN Prescriptions_clean
ON table1.PATID = Prescriptions_clean.PATID
WHERE (BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbi%') AND YEAR(FILL_DT) =
'2008' AND RowNumber = 1
GROUP BY table1.PATID
UNION
SELECT DISTINCT table1.PATID, MIN(FILL_DT) AS IndexDate
FROM ((SELECT DISTINCT Prescriptions_clean.PATID
FROM Prescriptions_clean INNER JOIN Indicator
ON Prescriptions_clean.PATID = Indicator.PATID
WHERE (BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbi%') AND YEAR(FILL_DT) =
'2009' AND RowNumber = 1 AND Indicator.Asthma = 1
INTERSECT
SELECT DISTINCT Prescriptions_clean.PATID
FROM Prescriptions_clean INNER JOIN Indicator
ON Prescriptions_clean.PATID = Indicator.PATID
WHERE YEAR(FILL_DT) = '2008' AND
MONTH(FILL_DT) < '6' AND Indicator.Asthma = 1)
EXCEPT
SELECT DISTINCT Prescriptions_clean.PATID
FROM Prescriptions_clean INNER JOIN Indicator
ON Prescriptions_clean.PATID = Indicator.PATID
WHERE (BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbi%') AND YEAR(FILL_DT) <
'2009' AND Indicator.Asthma = 1) AS table1 LEFT JOIN Prescriptions_clean
ON table1.PATID = Prescriptions_clean.PATID
WHERE (BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbi%') AND YEAR(FILL_DT) =
'2009' AND RowNumber = 1
GROUP BY table1.PATID
SELECT DISTINCT #ICS.PATID, MAX(Dose)
FROM #ICS LEFT JOIN
(SELECT DISTINCT #ICS.PATID, #ICS.IndexDate, Dose = CASE
WHEN McgPerDay IS NOT NULL THEN McgPerDay
WHEN McgPerDay IS NULL THEN 0 END
FROM #ICS LEFT JOIN Prescriptions_clean
ON #ICS.PATID = Prescriptions_clean.PATID
WHERE DATEDIFF(DAY, FILL_DT, IndexDate) < 365 AND DATEDIFF(DAY, FILL_DT,
IndexDate) >= 0 AND
(BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE
'azmacort%' OR BRND_NM LIKE 'budes%' OR BRND_NM LIKE 'pulmicort%' OR BRND_NM
LIKE 'qvar%' OR BRND_NM LIKE 'flovent%')) AS table2
ON #ICS.PATID = table2.PATID
GROUP BY #ICS.PATID
ORDER BY #ICS.PATID
DROP TABLE #ICS
```

31

```
SELECT DISTINCT table1.PracticeID, table1.PatientID, Sex, (2007-DOB) AS Age,
FEV1Predicted
FROM (SELECT DISTINCT derivedtbl_1.PracticeID, derivedtbl_1.PatientID,
derivedtbl_2.Sex, derivedtbl_2.FEV1Predicted
FROM (SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE (YEAR(DateIssued) = 2007 OR YEAR(DateIssued) = 2008 OR YEAR(DateIssued)
= 2009)) AS derivedtbl_1 INNER JOIN
(SELECT DISTINCT TOP (100) PERCENT tbl_practice_imports.PracticeID,
tbl_copd_data.PatientID, tbl_copd_data.Sex, MAX(CONVERT(float,
tbl_copd_data.Fev1Predicted)) AS FEV1Predicted
FROM tbl_copd_data INNER JOIN tbl_practice_imports
ON tbl_copd_data.importid = tbl_practice_imports.ID
WHERE (CONVERT(float, tbl_copd_data.Fev1Predicted) > 10) AND (CONVERT(float,
tbl_copd_data.Fev1Predicted) <= 100) AND (YEAR(tbl_copd_data.Fev1Date) = 2007
OR YEAR(tbl_copd_data.Fev1Date) = 2008 OR YEAR(tbl_copd_data.Fev1Date) = 2009)
GROUP BY tbl_practice_imports.PracticeID, tbl_copd_data.PatientID,
tbl_copd_data.Sex
```

```
ORDER BY tbl_practice_imports.PracticeID, tbl_copd_data.PatientID) AS
derivedtbl_2 ON derivedtbl_1.PracticeID = derivedtbl_2.PracticeID AND
derivedtbl_1.PatientID = derivedtbl_2.PatientID) AS table1 LEFT JOIN
(SELECT TOP (100) PERCENT PracticeID, PatientID, AVG(DOB) AS DOB
FROM (SELECT DISTINCT tbl_practice_imports_1.PracticeID,
tbl_copd_data_1.PatientID, tbl_copd_data_1.Sex, tbl_copd_data_1.AgeInYears,
tbl_practice_imports_1.ExportDate, YEAR(tbl_practice_imports_1.ExportDate) -
tbl_copd_data_1.AgeInYears AS DOB
FROM tbl_copd_data AS tbl_copd_data_1 INNER JOIN tbl_practice_imports AS
tbl_practice_imports_1 ON tbl_copd_data_1.importid =
tbl_practice_imports_1.ID) AS derivedtbl_1_1
GROUP BY PracticeID, PatientID
ORDER BY PracticeID, PatientID) AS table2
ON table1.PracticeID = table2.PracticeID AND table1.PatientID =
table2.PatientID
```

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```
SELECT DISTINCT PracticeID, PatientID, Sex, Age, Ratio
FROM (SELECT DISTINCT PracticeID, PatientID, Sex, Age, MAX(FEV1/FVC) AS Ratio
FROM (SELECT DISTINCT table1.PracticeID, table1.PatientID, Sex, (2007-DOB) AS
Age, FEV1, FVC
FROM (SELECT DISTINCT derivedtbl_1.PracticeID, derivedtbl_1.PatientID,
derivedtbl_2.Sex, derivedtbl_2.FEV1, derivedtbl_2.FVC
FROM (SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE (YEAR(DateIssued) = 2007 OR YEAR(DateIssued) = 2008 OR YEAR(DateIssued)
= 2009)) AS derivedtbl_1 INNER JOIN
(SELECT DISTINCT TOP (100) PERCENT tbl_practice_imports.PracticeID,
tbl_copd_data.PatientID, tbl_copd_data.Sex, MAX(CONVERT(float,
tbl_copd_data.Fev1)) AS FEV1, MAX(CONVERT(float, tbl_copd_data.Fvc)) AS FVC
FROM tbl_copd_data INNER JOIN tbl_practice_imports
ON tbl_copd_data.importid = tbl_practice_imports.ID
WHERE (YEAR(tbl_copd_data.Fev1Date) = 2007 OR YEAR(tbl_copd_data.Fev1Date) =
2008 OR YEAR(tbl_copd_data.Fev1Date) = 2009)
GROUP BY tbl_practice_imports.PracticeID, tbl_copd_data.PatientID,
tbl_copd_data.Sex
ORDER BY tbl_practice_imports.PracticeID, tbl_copd_data.PatientID) AS
derivedtbl_2 ON derivedtbl_1.PracticeID = derivedtbl_2.PracticeID AND
derivedtbl_1.PatientID = derivedtbl_2.PatientID) AS table1 LEFT JOIN
(SELECT TOP (100) PERCENT PracticeID, PatientID, AVG(DOB) AS DOB
FROM (SELECT DISTINCT tbl_practice_imports_1.PracticeID,
tbl_copd_data_1.PatientID, tbl_copd_data_1.Sex, tbl_copd_data_1.AgeInYears,
tbl_practice_imports_1.ExportDate, YEAR(tbl_practice_imports_1.ExportDate) -
tbl_copd_data_1.AgeInYears AS DOB
FROM tbl_copd_data AS tbl_copd_data_1 INNER JOIN tbl_practice_imports AS
tbl_practice_imports_1 ON tbl_copd_data_1.importid =
tbl_practice_imports_1.ID) AS derivedtbl_1_1
GROUP BY PracticeID, PatientID
ORDER BY PracticeID, PatientID) AS table2
ON table1.PracticeID = table2.PracticeID AND table1.PatientID =
table2.PatientID
WHERE FEV1 IS NOT NULL AND FVC IS NOT NULL AND FEV1 <> '0' AND FVC <> '0') AS
table3
GROUP BY PracticeID, PatientID, Age, Sex) AS table4
```

33

```
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
((DrugName LIKE 'Salbutamol%' AND (Preparation NOT LIKE '%SOLN%' AND
Preparation NOT LIKE '%TABS%')) OR (DrugName LIKE 'Terbutaline%') OR
(DrugName LIKE 'Ipratrop%') OR (DrugName LIKE 'Combivent%'))
EXCEPT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Seretide%' OR DrugName LIKE 'Symbicort%' OR DrugName LIKE
'Salmeterol%' OR DrugName LIKE 'Formoterol%' OR DrugName LIKE 'Beclometa%' OR
DrugName LIKE 'Budes%' OR DrugName LIKE 'Cicles%' OR DrugName LIKE 'clenil%'
OR DrugName LIKE 'Flutica%' OR DrugName LIKE 'Mometa%' OR DrugName LIKE
'Qvar%' OR DrugName LIKE 'Tiotrop%')
```

34

```
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Salmeterol%' OR DrugName LIKE 'Formoterol%')
```

```
EXCEPT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Seretide%' OR DrugName LIKE 'Symbicort%' OR DrugName LIKE
'Beclometa%' OR DrugName LIKE 'Budes%' OR DrugName LIKE 'Cicles%' OR DrugName
LIKE 'clenil%' OR DrugName LIKE 'Flutica%' OR DrugName LIKE 'Mometa%' OR
DrugName LIKE 'Qvar%' OR DrugName LIKE 'Tiotrop%')
```

35

```
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Tiotrop%')
EXCEPT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Seretide%' OR DrugName LIKE 'Symbicort%' OR DrugName LIKE
'Beclometa%' OR DrugName LIKE 'Budes%' OR DrugName LIKE 'Cicles%' OR DrugName
LIKE 'clenil%' OR DrugName LIKE 'Flutica%' OR DrugName LIKE 'Mometa%' OR
DrugName LIKE 'Qvar%' OR DrugName LIKE 'Salmeterol%' OR
DrugName LIKE 'Formoterol%')
```

36

```
((SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Salmeterol%' OR DrugName LIKE 'Formoterol%')
INTERSECT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Beclometa%' OR DrugName LIKE 'Budes%' OR DrugName LIKE
'Cicles%' OR DrugName LIKE 'clenil%' OR DrugName LIKE 'Flutica%' OR DrugName
LIKE 'Mometa%' OR DrugName LIKE 'Qvar%'))
UNION
(SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Seretide%' OR DrugName LIKE 'Symbicort%')))
EXCEPT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Tiotrop%')
```

37

```
(SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Salmeterol%' OR DrugName LIKE 'Formoterol%')
INTERSECT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Tiotrop%'))
EXCEPT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Beclometa%' OR DrugName LIKE 'Budes%' OR DrugName LIKE
'Cicles%' OR DrugName LIKE 'clenil%' OR DrugName LIKE 'Flutica%' OR DrugName
LIKE 'Mometa%' OR DrugName LIKE 'Qvar%' OR DrugName LIKE 'Seretide%' OR
DrugName LIKE 'Symbic%')
```

38

```
(((SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Salmeterol%' OR DrugName LIKE 'Formoterol%')
INTERSECT
SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Beclometa%' OR DrugName LIKE 'Budes%' OR DrugName LIKE
'Cicles%' OR DrugName LIKE 'clenil%' OR DrugName LIKE 'Flutica%' OR DrugName
LIKE 'Mometa%' OR DrugName LIKE 'Qvar%'))
```

```
UNION
(SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Seretide%' OR DrugName LIKE 'Symbicort%'))))
INTERSECT
(SELECT DISTINCT PracticeID, PatientID
FROM tbl_copd_prescriptions
WHERE YEAR(DateIssued) = '2008' AND
(DrugName LIKE 'Tiotrop%'))
```

39

```
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'accuneb' OR (BRND_NM LIKE 'Albuterol%' AND (STRENGTH NOT
LIKE '2MG%' OR STRENGTH NOT LIKE '4MG%' OR STRENGTH NOT LIKE '5MG%' OR
STRENGTH <> '8MG')) OR BRND_NM LIKE 'maxair%' OR BRND_NM LIKE 'proair%' OR
BRND_NM LIKE 'ventolin%' OR BRND_NM LIKE 'xopenex%' OR BRND_NM LIKE 'atrovent
HFA%' OR BRND_NM LIKE 'combivent%' OR BRND_NM LIKE 'duoneb%' OR BRND_NM LIKE
'ipratropium-albuterol%' OR (BRND_NM LIKE 'ipratrop%' AND (STRENGTH NOT LIKE
'21MCG%' OR STRENGTH NOT LIKE '42MCG%')))
AND Indicator.PATID NOT IN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE
'azmacort%' OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE 'pulmicort flexhaler%'
OR BRND_NM LIKE 'pulmicort  %' OR BRND_NM LIKE 'budesonide%' OR BRND_NM LIKE
'qvar%' OR BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%' OR BRND_NM LIKE
'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE 'perforomist%' OR
BRND_NM LIKE 'serevent%' OR BRND_NM LIKE 'spiriva%'))
```

40

```
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE
'perforomist%' OR BRND_NM LIKE 'serevent%')
AND Indicator.PATID NOT IN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE
'azmacort%' OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE 'pulmicort flexhaler%'
OR BRND_NM LIKE 'pulmicort  %' OR BRND_NM LIKE 'budesonide%' OR BRND_NM LIKE
'qvar%' OR BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%' OR BRND_NM LIKE
'spiriva%'))
```

41

```
SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'spiriva%')
AND Indicator.PATID NOT IN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
```

```
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE
'azmacort%' OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE 'pulmicort flexhaler%'
OR BRND_NM LIKE 'pulmicort  %' OR BRND_NM LIKE 'budesonide%' OR BRND_NM LIKE
'qvar%' OR BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%' OR BRND_NM LIKE
'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE 'perforomist%' OR
BRND_NM LIKE 'serevent%'))
```

42

```
SELECT DISTINCT table3.PATID
FROM ((SELECT DISTINCT table1.PATID
FROM (SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE
'perforomist%' OR BRND_NM LIKE 'serevent%')) as table1 INNER JOIN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE
'azmacort%' OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE 'pulmicort flexhaler%'
OR BRND_NM LIKE 'pulmicort  %' OR BRND_NM LIKE 'budesonide%' OR BRND_NM LIKE
'qvar%')) as table2
ON table1.PATID = table2.PATID)
UNION
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%'))) as table3
WHERE table3.PATID NOT IN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'spiriva%'))
```

43

```
SELECT DISTINCT table1.PATID
FROM (SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE
'perforomist%' OR BRND_NM LIKE 'serevent%')) as table1 INNER JOIN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'spiriva%')) as table2
ON table1.PATID = table2.PATID
WHERE table1.PATID NOT IN
```

```
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE
'azmacort%' OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE 'pulmicort flexhaler%'
OR BRND_NM LIKE 'pulmicort  %' OR BRND_NM LIKE 'budesonide%' OR BRND_NM LIKE
'qvar%' OR BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%'))
```

44

```
SELECT DISTINCT table4.PATID
FROM ((SELECT DISTINCT table1.PATID
FROM (SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'brovana%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE
'perforomist%' OR BRND_NM LIKE 'serevent%')) as table1 INNER JOIN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'aerobid%' OR BRND_NM LIKE 'asmanex%' OR BRND_NM LIKE
'azmacort%' OR BRND_NM LIKE 'flovent%' OR BRND_NM LIKE 'pulmicort flexhaler%'
OR BRND_NM LIKE 'pulmicort  %' OR BRND_NM LIKE 'budesonide%' OR BRND_NM LIKE
'qvar%')) as table2
ON table1.PATID = table2.PATID)
UNION
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'advair%' OR BRND_NM LIKE 'symbicort%'))) as table3 INNER
JOIN
(SELECT DISTINCT Indicator.PATID
FROM Indicator INNER JOIN Overall
ON Indicator.PATID = Overall.PATID
INNER JOIN Prescriptions_clean
ON Prescriptions_clean.PATID = Overall.PATID
WHERE (Indicator.Chronic_bronchitis = 1 OR Indicator.Emphysema = 1 OR
Indicator.COPD = 1) AND DATEPART(year, Prescriptions_clean.FILL_DT) = '2008'
AND (BRND_NM LIKE 'spiriva%')) as table4
ON table3.PATID = table4.PATID
```

45

```
SELECT DISTINCT *
FROM tbl_copd_prescriptions_date
WHERE (DrugName LIKE 'seretide%') AND
(YEAR(DateIssued) = '2007' OR YEAR(DateIssued) = '2008' OR YEAR(DateIssued) =
'2009') AND McgPerDay = '1000' AND Preparation LIKE '500 accuhaler%'
```

46

```
SELECT DISTINCT *
FROM Prescriptions_clean INNER JOIN Indicator
ON Indicator.PATID = Prescriptions_clean.PATID
WHERE (Indicator.COPD = 1 OR Indicator.Chronic_bronchitis = 1 OR
Indicator.Emphysema = 1)
AND (BRND_NM LIKE 'advair%') AND
(YEAR(FILL_DT) = '2007' OR YEAR(FILL_DT) = '2008' OR YEAR(FILL_DT) = '2009')
AND McgPerDay = '500' AND BRND_NM LIKE '%diskus%' AND STRENGTH LIKE '250%
```

47

```
SELECT *
FROM (SELECT DISTINCT table1.PracticeID, table1.PatientID
FROM (SELECT DISTINCT PracticeID, PatientID, DateIssued AS DateIssued1
FROM tbl_copd_prescriptions_date
```

```
WHERE (DrugName LIKE 'budes%') AND
(YEAR(DateIssued) = '2007')) AS table1 INNER JOIN
(SELECT DISTINCT PracticeID, PatientID, DateIssued AS DateIssued2
FROM tbl_copd_prescriptions_date
WHERE (DrugName LIKE 'salmeterol%' OR DrugName LIKE 'formoterol%')) AS table2
ON table1.PracticeID = table2.PracticeID AND table1.PatientID =
table2.PatientID
WHERE DATEDIFF(day, DateIssued1, DateIssued2) <= 100 AND DATEDIFF(day,
DateIssued1, DateIssued2) >= -100) AS table3 LEFT JOIN
(SELECT *
FROM tbl_copd_prescriptions_date
WHERE (DrugName LIKE 'budes%') AND
(YEAR(DateIssued) = '2007')) AS table4
ON table3.PracticeID = table4.PracticeID AND table3.PatientID =
table4.PatientID
ORDER BY McgPerDay
```

48

```
SELECT *
FROM (SELECT DISTINCT table1.PATID
FROM (SELECT DISTINCT Prescriptions_clean.PATID, FILL_DT AS DateIssued1
FROM Prescriptions_clean INNER JOIN Indicator
ON Indicator.PATID = Prescriptions_clean.PATID
WHERE (Indicator.COPD = 1 OR Indicator.Chronic_bronchitis = 1 OR
Indicator.Emphysema = 1)
AND (BRND_NM LIKE 'qvar%') AND
(YEAR(FILL_DT) = '2009')) AS table1 INNER JOIN
(SELECT DISTINCT Prescriptions_clean.PATID, FILL_DT AS DateIssued2
FROM Prescriptions_clean INNER JOIN Indicator
ON Indicator.PATID = Prescriptions_clean.PATID
WHERE (Indicator.COPD = 1 OR Indicator.Chronic_bronchitis = 1 OR
Indicator.Emphysema = 1)
AND (BRND_NM LIKE 'serevent%' OR BRND_NM LIKE 'foradil%' OR BRND_NM LIKE
'perforo%' OR BRND_NM LIKE 'brovana%')) AS table2
ON table1.PATID = table2.PATID
WHERE DATEDIFF(day, DateIssued1, DateIssued2) <= 100 AND DATEDIFF(day,
DateIssued1, DateIssued2) >= -100) AS table3 LEFT JOIN
(SELECT DISTINCT Prescriptions_clean.PATID, BRND_NM, STRENGTH, FILL_DT,
McgPerDay
FROM Prescriptions_clean INNER JOIN Indicator
ON Indicator.PATID = Prescriptions_clean.PATID
WHERE (Indicator.COPD = 1 OR Indicator.Chronic_bronchitis = 1 OR
Indicator.Emphysema = 1)
AND (BRND_NM LIKE 'qvar%') AND
(YEAR(FILL_DT) = '2009')) AS table4
ON table3.PATID = table4.PATID
ORDER BY McgPerDay
```

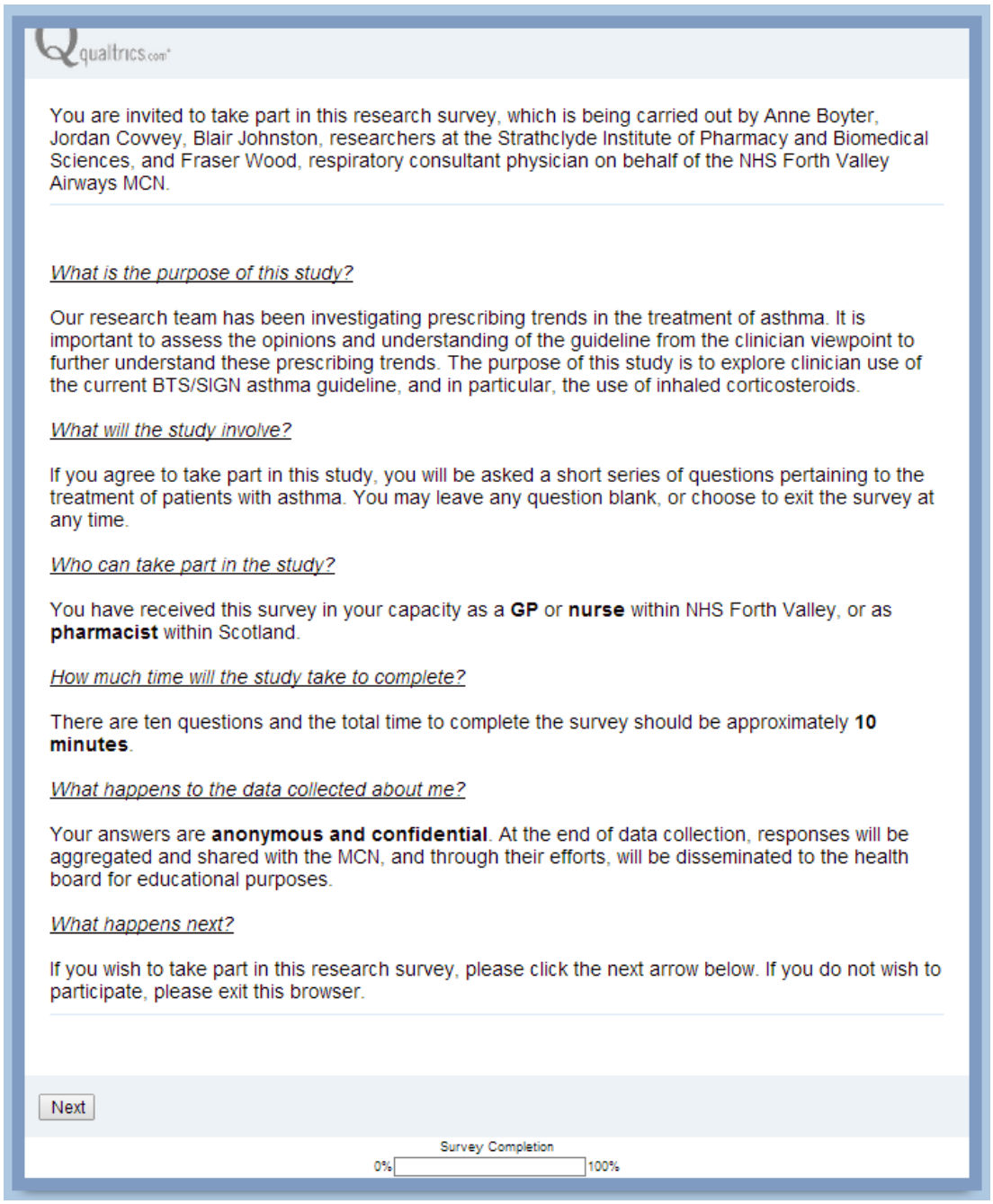
49

```
SELECT DISTINCT PracticeID, PatientID, Sex, Age, YEAR(FEV1), YEAR(DateIssued),
Diff
FROM (SELECT DISTINCT derivedtbl_1.PracticeID, derivedtbl_1.PatientID,
derivedtbl_2.Sex, derivedtbl_2.Age, MIN(Fev1Date) AS FEV1, MIN(DateIssued) AS
DateIssued, DATEDIFF(Day, MIN(DateIssued), MIN(Fev1Date)) AS Diff
FROM (SELECT tbl_practice_imports.PracticeID, tbl_copd_data.PatientID,
tbl_copd_data.Fev1Date
FROM tbl_copd_data INNER JOIN tbl_practice_imports ON tbl_copd_data.importid =
tbl_practice_imports.ID
) AS derivedtbl_1 INNER JOIN
(SELECT derivedtbl_1_2.PracticeID, derivedtbl_1_2.PatientID, Sex, 2009 -
derivedtbl_2_1.DOB AS Age, DateIssued
FROM (SELECT DISTINCT PracticeID, PatientID, DateIssued
FROM tbl_copd_prescriptions
WHERE (YEAR(DateIssued) = '2009')) AS derivedtbl_1_2 INNER JOIN
(SELECT DISTINCT PracticeID, PatientID, Sex, AVG(DOB) AS DOB
FROM (SELECT DISTINCT tbl_practice_imports_1.PracticeID,
tbl_copd_data_1.PatientID, tbl_copd_data_1.Sex, tbl_copd_data_1.AgeInYears,
tbl_practice_imports_1.ExportDate, YEAR(tbl_practice_imports_1.ExportDate) -
tbl_copd_data_1.AgeInYears AS DOB
FROM tbl_copd_data AS tbl_copd_data_1 INNER JOIN
tbl_practice_imports AS tbl_practice_imports_1 ON tbl_copd_data_1.importid =
tbl_practice_imports_1.ID) AS derivedtbl_1_1
GROUP BY PracticeID, PatientID, Sex) AS derivedtbl_2_1 ON
derivedtbl_1_2.PracticeID = derivedtbl_2_1.PracticeID AND
derivedtbl_1_2.PatientID = derivedtbl_2_1.PatientID) AS derivedtbl_2 ON
derivedtbl_1.PracticeID = derivedtbl_2.PracticeID AND  derivedtbl_1.PatientID
```

```
= derivedtbl_2.PatientID
GROUP BY derivedtbl_1.PracticeID, derivedtbl_1.PatientID, Sex, Age
HAVING MIN(Fev1Date) IS NULL
UNION
SELECT DISTINCT derivedtbl_1.PracticeID, derivedtbl_1.PatientID,
derivedtbl_2.Sex, derivedtbl_2.Age, MIN(Fev1Date) AS FEV1, MIN(DateIssued) AS
DateIssued, DATEDIFF(Day, MIN(DateIssued), MIN(Fev1Date)) AS Diff
FROM (SELECT tbl_practice_imports.PracticeID, tbl_copd_data.PatientID,
tbl_copd_data.Fev1Date
FROM tbl_copd_data INNER JOIN tbl_practice_imports ON tbl_copd_data.importid =
tbl_practice_imports.ID
) AS derivedtbl_1 INNER JOIN
(SELECT derivedtbl_1_2.PracticeID, derivedtbl_1_2.PatientID, Sex, 2009 -
derivedtbl_2_1.DOB AS Age, DateIssued
FROM (SELECT DISTINCT PracticeID, PatientID, DateIssued
FROM tbl_copd_prescriptions
WHERE (YEAR(DateIssued) = '2009')) AS derivedtbl_1_2 INNER JOIN
(SELECT DISTINCT PracticeID, PatientID, Sex, AVG(DOB) AS DOB
FROM (SELECT DISTINCT tbl_practice_imports_1.PracticeID,
tbl_copd_data_1.PatientID, tbl_copd_data_1.Sex, tbl_copd_data_1.AgeInYears,
tbl_practice_imports_1.ExportDate, YEAR(tbl_practice_imports_1.ExportDate) -
tbl_copd_data_1.AgeInYears AS DOB
FROM tbl_copd_data AS tbl_copd_data_1 INNER JOIN
tbl_practice_imports AS tbl_practice_imports_1 ON tbl_copd_data_1.importid =
tbl_practice_imports_1.ID) AS derivedtbl_1_1
GROUP BY PracticeID, PatientID, Sex) AS derivedtbl_2_1 ON
derivedtbl_1_2.PracticeID = derivedtbl_2_1.PracticeID AND
derivedtbl_1_2.PatientID = derivedtbl_2_1.PatientID) AS derivedtbl_2 ON
derivedtbl_1.PracticeID = derivedtbl_2.PracticeID AND  derivedtbl_1.PatientID
= derivedtbl_2.PatientID
GROUP BY derivedtbl_1.PracticeID, derivedtbl_1.PatientID, Sex, Age
HAVING DATEDIFF(Day, MIN(DateIssued), MIN(Fev1Date)) > -365 AND DATEDIFF(Day,
MIN(DateIssued), MIN(Fev1Date)) < 183) AS table1
ORDER BY PracticeID, PatientID
```

Appendix IV: Clinician survey on asthma

Clinician survey questions (introduction)



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You are invited to take part in this research survey, which is being carried out by Anne Boyter, Jordan Covvey, Blair Johnston, researchers at the Strathclyde Institute of Pharmacy and Biomedical Sciences, and Fraser Wood, respiratory consultant physician on behalf of the NHS Forth Valley Airways MCN.

What is the purpose of this study?

Our research team has been investigating prescribing trends in the treatment of asthma. It is important to assess the opinions and understanding of the guideline from the clinician viewpoint to further understand these prescribing trends. The purpose of this study is to explore clinician use of the current BTS/SIGN asthma guideline, and in particular, the use of inhaled corticosteroids.

What will the study involve?

If you agree to take part in this study, you will be asked a short series of questions pertaining to the treatment of patients with asthma. You may leave any question blank, or choose to exit the survey at any time.

Who can take part in the study?

You have received this survey in your capacity as a **GP** or **nurse** within NHS Forth Valley, or as **pharmacist** within Scotland.

How much time will the study take to complete?

There are ten questions and the total time to complete the survey should be approximately **10 minutes**.

What happens to the data collected about me?

Your answers are **anonymous and confidential**. At the end of data collection, responses will be aggregated and shared with the MCN, and through their efforts, will be disseminated to the health board for educational purposes.

What happens next?

If you wish to take part in this research survey, please click the next arrow below. If you do not wish to participate, please exit this browser.

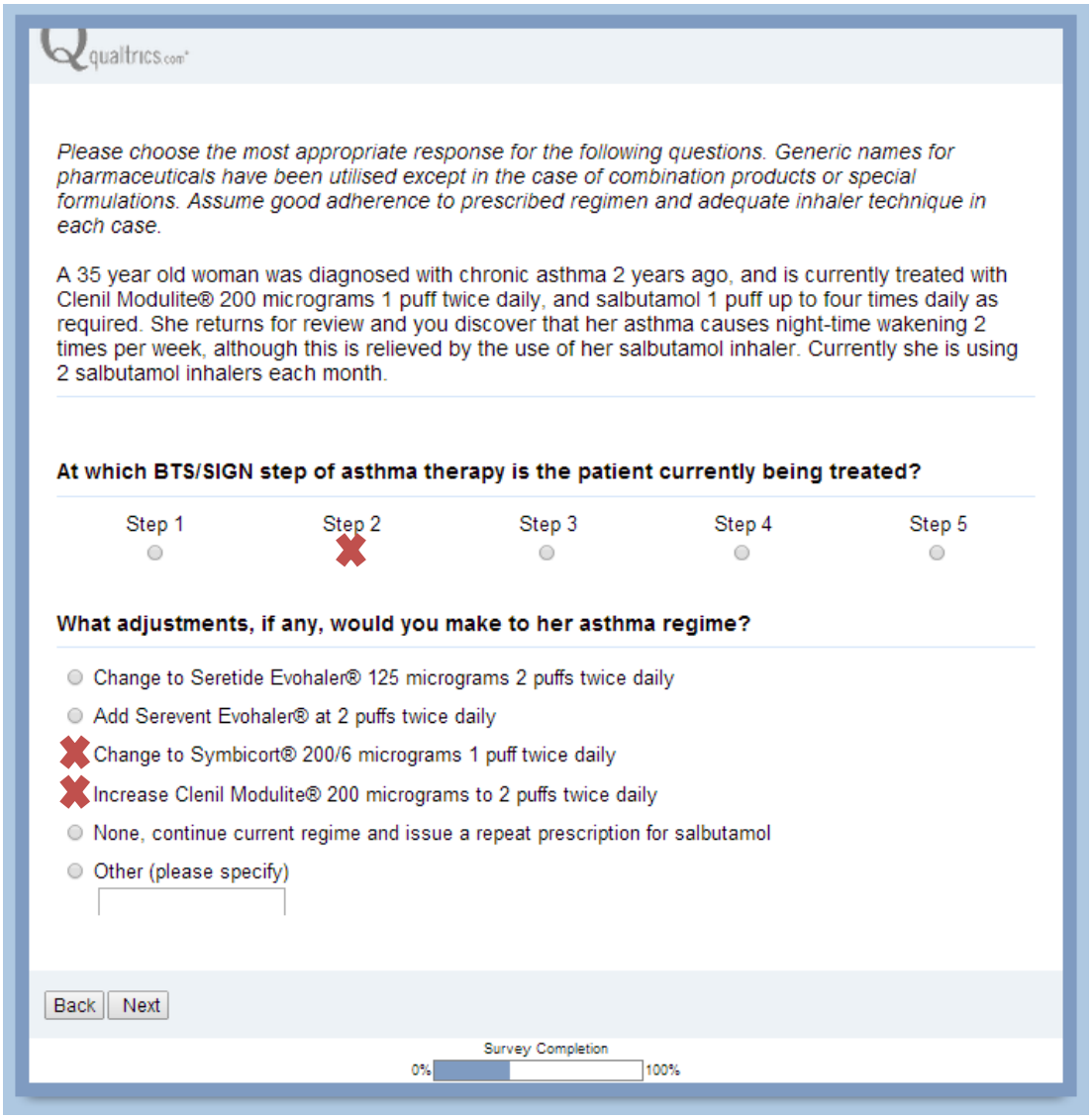
Next

Survey Completion

0% 100%

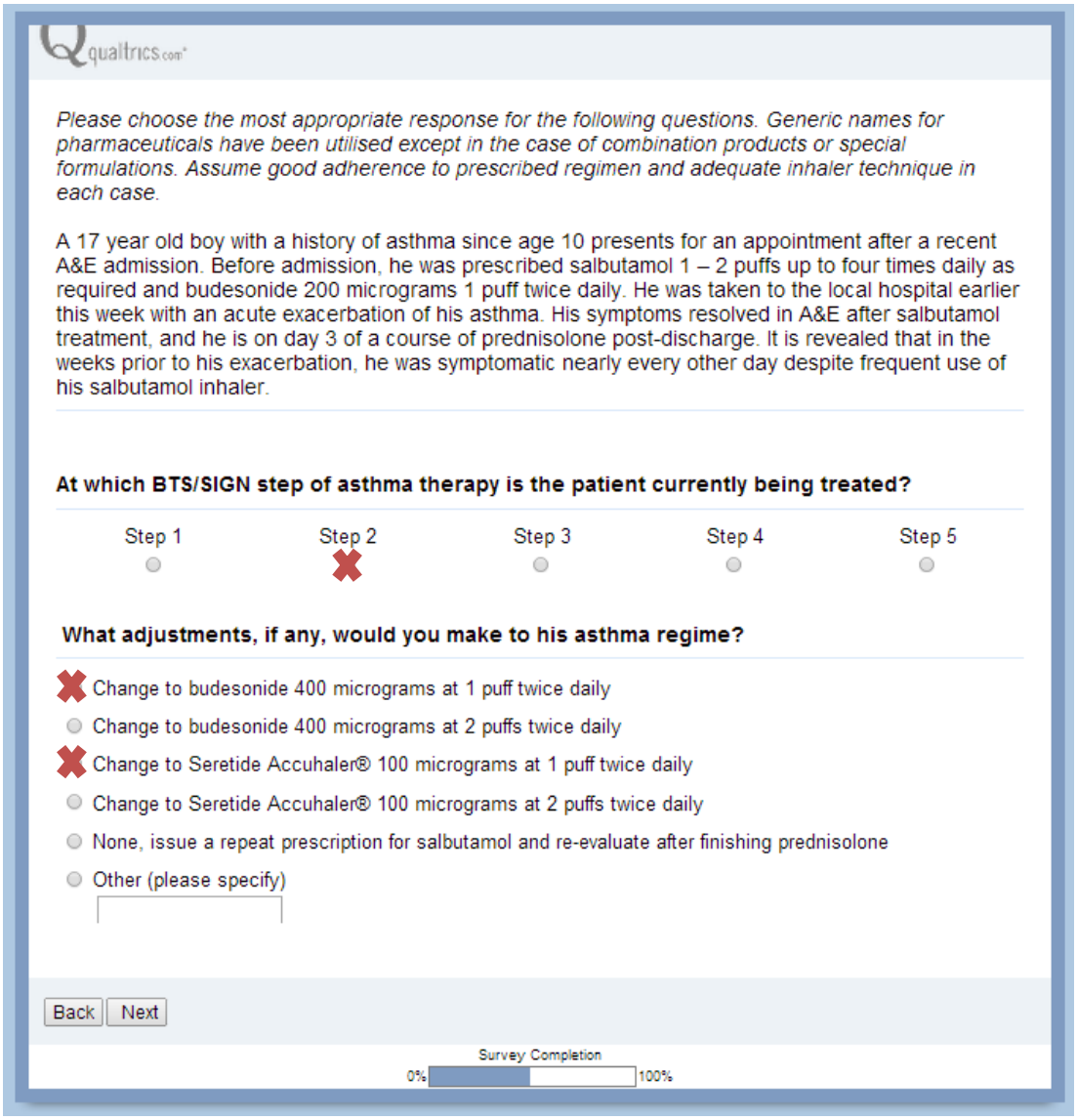
Clinician survey questions (case based)

Case 1 and questions 1.1 and 1.2
Crosses indicate most appropriate choices



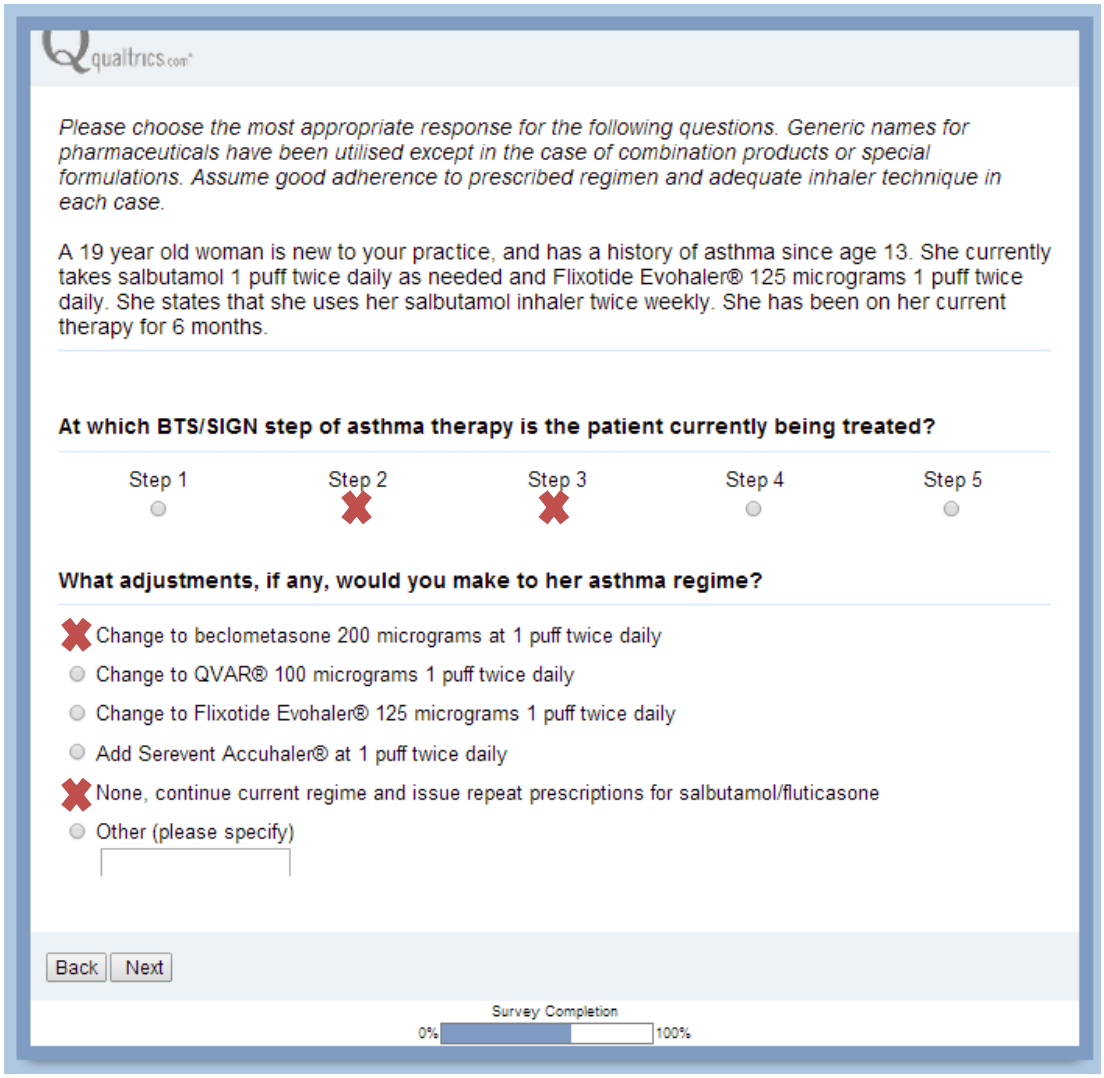
Clinician survey questions (case based), cont.

Case 2 and questions 2.1 and 2.2
Crosses indicate most appropriate choices



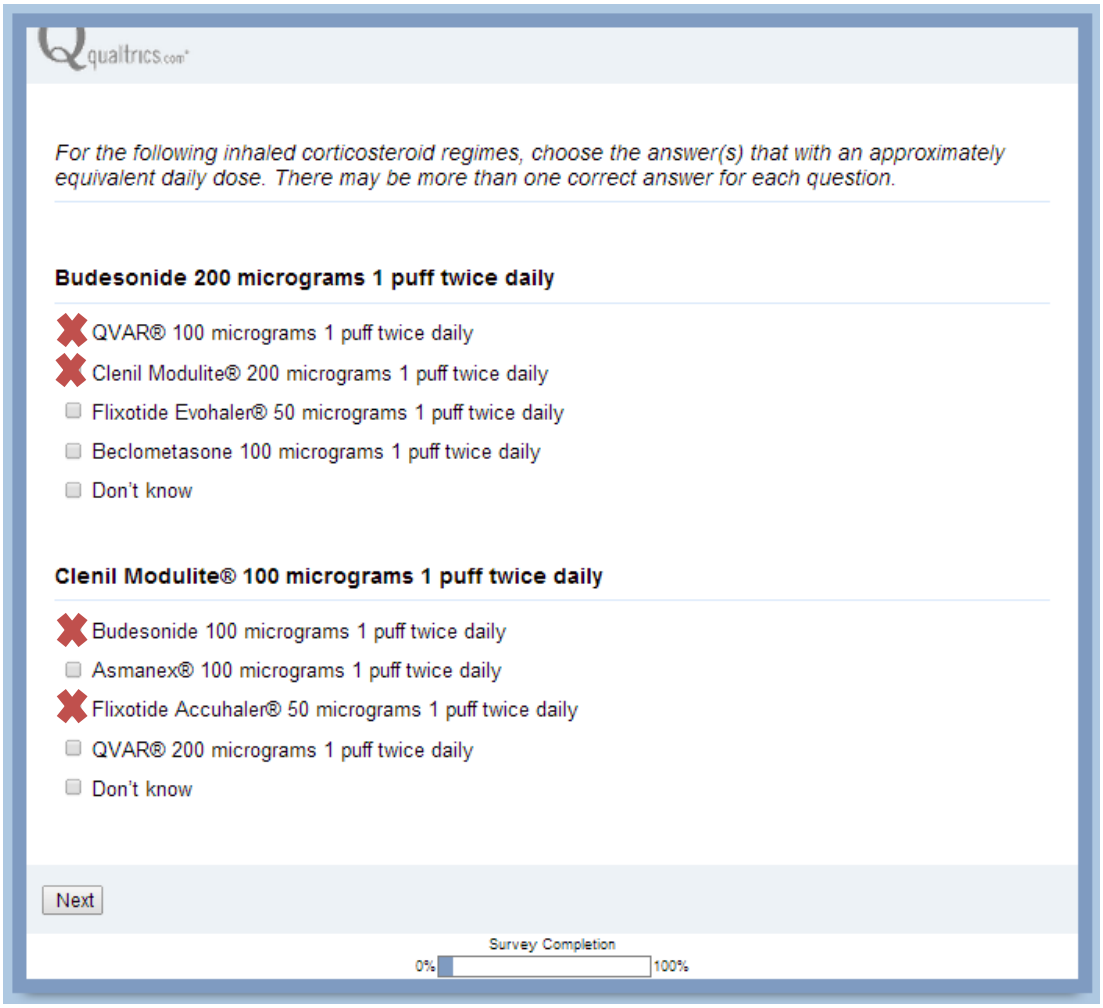
Clinician survey questions (case based), cont.

Case 3 and questions 3.1 and 3.2
Crosses indicate most appropriate choices



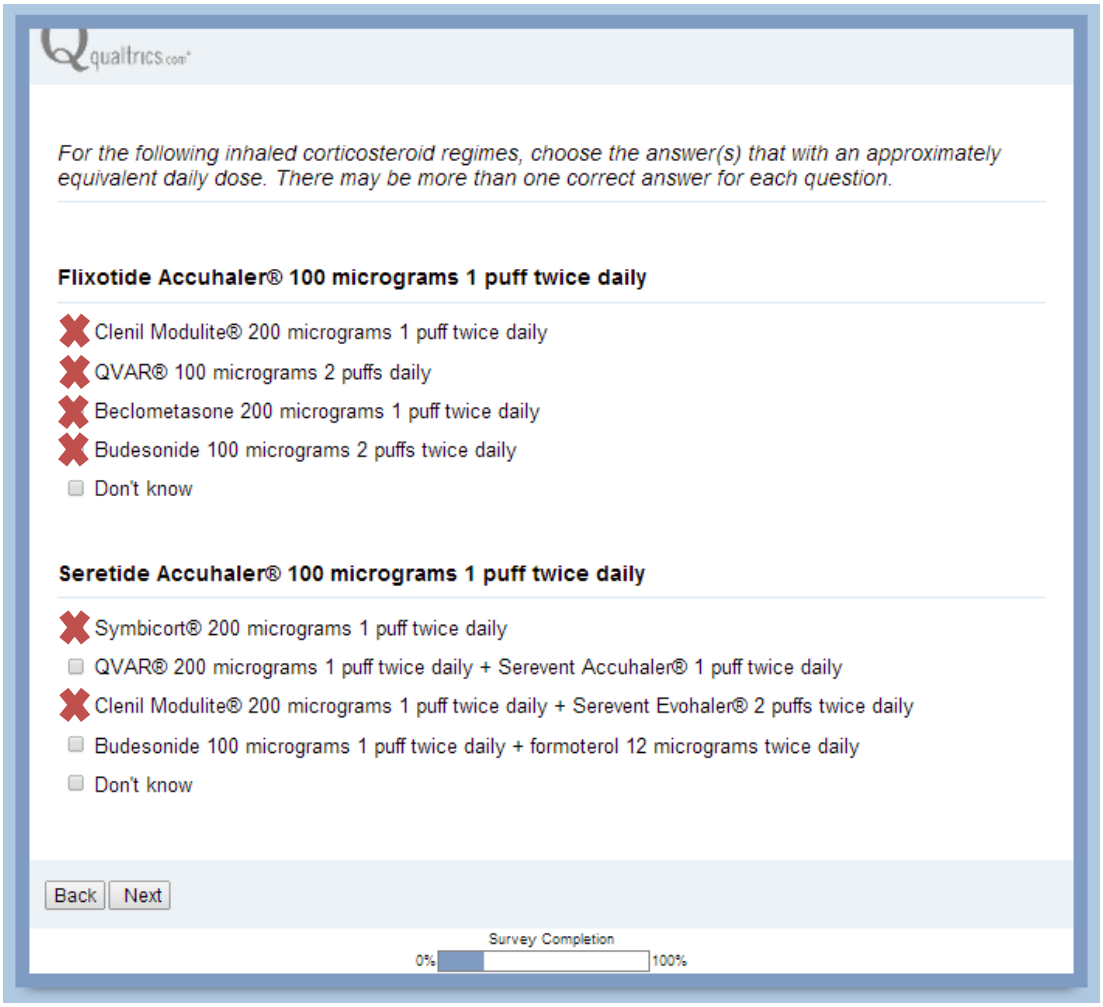
Clinician survey questions (multiple-response)

Questions 4.1 and 4.2
Crosses indicate most appropriate choices

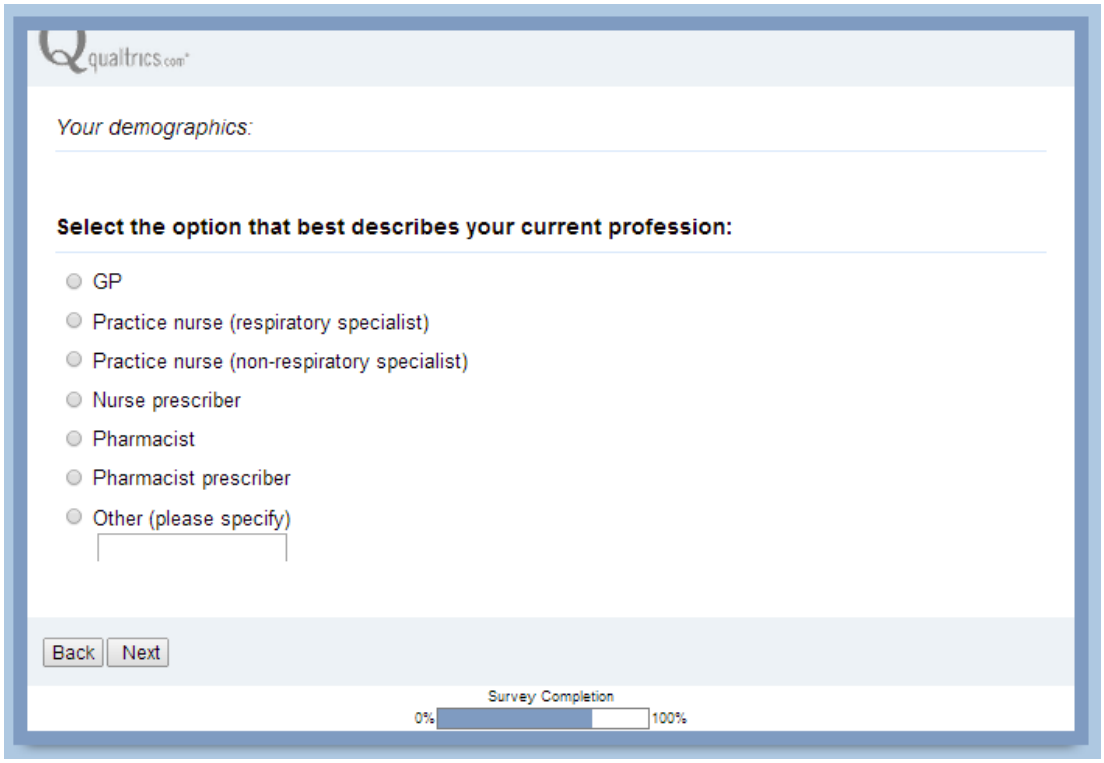


Clinician survey questions (multiple-response), cont.

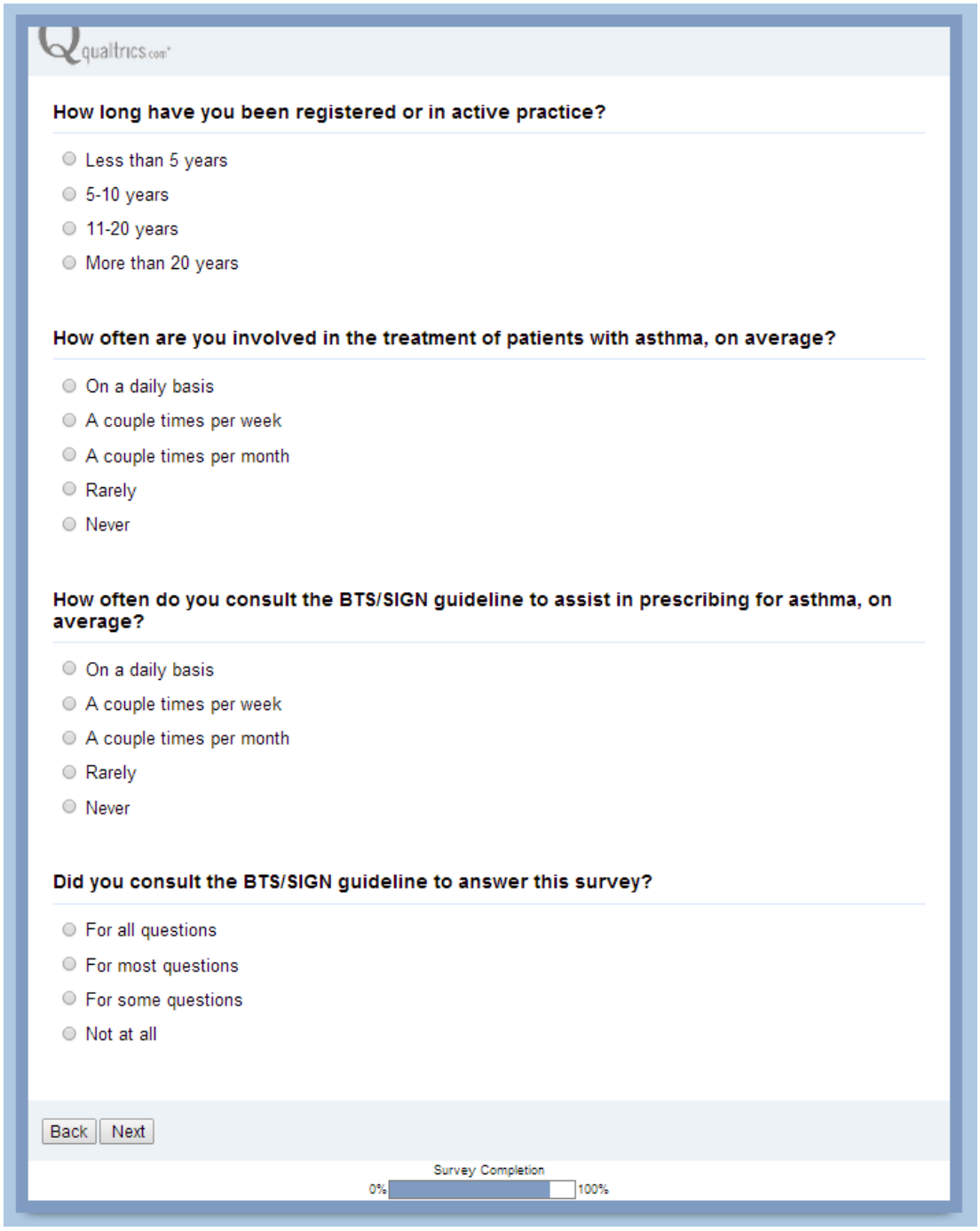
Questions 4.3 and 4.4
Crosses indicate most appropriate choices



Clinician survey questions (demographics)
Question 5



Clinician survey questions (demographics), cont.
Questions 6, 7, 8 and 9



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How long have you been registered or in active practice?

- Less than 5 years
- 5-10 years
- 11-20 years
- More than 20 years

How often are you involved in the treatment of patients with asthma, on average?

- On a daily basis
- A couple times per week
- A couple times per month
- Rarely
- Never

How often do you consult the BTS/SIGN guideline to assist in prescribing for asthma, on average?

- On a daily basis
- A couple times per week
- A couple times per month
- Rarely
- Never

Did you consult the BTS/SIGN guideline to answer this survey?

- For all questions
- For most questions
- For some questions
- Not at all

Back Next

Survey Completion
0% 100%

Appendix V: Publications

Peer-reviewed journal manuscripts

- Covvey JR, Mullen AB, Ryan M, Steinke DT, Johnston BF, Wood FT and Boyter AC. (2014). A comparison of medication adherence/persistence for asthma and chronic obstructive pulmonary disease in the United Kingdom. *Int J Clin Pract*. Published online first: 2014 May 5. http://dx.doi.org/10.1111/ijcp.12451
- Covvey JR, Johnston BF, Wood F and Boyter AC. (2014). Changes to inhaled corticosteroid dose when initiating combination inhaler therapy in long-acting beta agonist naïve patients with asthma: a retrospective database analysis. *Thorax*. Published online first: 2014 Jan 15. http://dx.doi.org/10.1136/thoraxjnl-2013-204944
- Covvey JR, Johnston BF, Wood F and Boyter AC. (2013). Retrospective database analysis of asthma therapy: is the guideline confusing? *Prim Care Respir J*;22(3):290-295. http://dx.doi.org/10.4104/pcrj.2013.00060

Peer-reviewed poster presentations

- Covvey JR, Johnston BF and Boyter AC. (2014). Do patients take their medicine? A comparison of adherence and persistence with inhalers in patients with respiratory disease. *University Research Day; University of Strathclyde.*
- Covvey JR, Mullen AB, Johnston BF, Wood FT and Boyter AC. (2014). A comparison of adherence and persistence with inhaled therapies in patients with asthma or chronic obstructive pulmonary disease in the United Kingdom. *ACCP Virtual Poster Symposium.*
- Covvey JR, Johnston BF and Boyter AC. (2012). Characterising asthma therapy in Scotland: are the guidelines confusing? *Eur Respir J*; 40: Suppl. 56, 106s.
- Covvey JR, Johnston BF and Boyter AC. (2012). Characterisation of COPD patients in Scotland. *Eur Respir J*; 40: Suppl. 56, 495s.
- Covvey JR, Johnston BF and Boyter AC. (2012). Characterising asthma therapy in Scotland: are the guidelines confusing? *University Research Day; University of Strathclyde.*