University of Sheffield

TRAINS Project:

TRial to

Assess

Implementation of

New research in a primary care

Setting

A pragmatic cluster randomised controlled trial (cRCT) of an educational intervention to promote asthma prescription uptake in General Practitioner Practices

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

University of Sheffield

School of Health and Related Research

Author:
Rami A. Alyami

Supervisors:
Prof. Steven A. Julious
Dr. Rebecca M. Simpson
Dr. Phillip Oliver

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Abstract

Background: Asthma exacerbation rates in school-age children peak following the return to school after the summer break. Studies have shown a decline in prescriptions collection during August, which is followed by an increase in unscheduled visits to healthcare providers. A previous study (the PLEASANT trial) found that sending reminder letters to parents of children with asthma during the summer vacation led to a 30% increase in August prescriptions being prescribed and reduced unscheduled care visits after the return to schools in the period September to December. The intervention also resulted in an estimated cost saving of £36.07 per patient per year.

Objective: To determine if informing general practitioner (GP) practices about the PLEASANT trial intervention results leads to its implementation.

Design: A pragmatic cluster randomised trial which utilised the Clinical Practice Research Datalink (CPRD) to send the intervention and collect data.

Participants: A total of 1,326 GP practices in England, including 90,583 individuals, with 664 practices (44,708 individuals) in the intervention group and 662 practices (45,875 individuals) in the control group.

Intervention: In June 2021, the intervention practices received a letter from CPRD about the PLEASANT study findings and recommendations. The letter was sent to the asthma lead and/or practice manager via postal mail and email.

Control Arm: Usual care.

Randomisation: GP practices were stratified by practice size (decile) and randomly allocated to either the intervention or control group.

Main Outcome: The proportion of children with asthma who had a prescription for an asthma preventer medication in August and September 2021.

Results: The intervention did not significantly affect the proportion of children with asthma who had a prescription in August and September 2021 compared to the control arm. In the intervention group, 15,716 out of 44,465 children (35.3%) had a prescription issued, compared to 16,001 out of 45,559 children (35.1%) in the control group (OR 1.01; 95% CI: 0.97 to 1.04). There was also no intervention effect on the uptake of prescriptions in the same period (IRR 1.01; 95% CI: 0.98 to 1.03). Furthermore, the letter did not reduce the number of unscheduled medical contacts after returning to school from September to December 2021 (IRR 0.99; 95% CI: 0.96 to 1.02) and all medical contacts remained unchanged (IRR 1.00; 95% CI: 0.97 to 1.02).

Conclusion: The study findings suggest that passive intervention of providing a letter to GPs did not achieve the intended outcomes. To bridge the gap between evidence and practice, alternative, more proactive strategies could be explored to address the identified issues.

Conferences and publications

Papers

Alyami, R.A., Simpson, R., Oliver, P. and Julious, S.A., 2022. TRial to Assess Implementation of New research in a primary care Setting (TRAINS): study protocol for a pragmatic cluster randomised controlled trial of an educational intervention to promote asthma prescription uptake in general practitioner practices. Trials, 23(1), p.947

Oral Presentations

Alyami R, Julious S, Simpson R, Oliver P. TRAINS: A Pragmatic Cluster RCT to Prevent Summer Holiday Drop in Asthma Prescription Uptake in School-Age Children. *The 51st Annual Scientific Meeting of Society for Academic Primary Care (SAPC)*. 18-19 July 2023, Brighton, UK.

Alyami R, Julious S, Simpson R, Oliver P. A Pragmatic Cluster RCT of a Letter to GPs to Stop Decline in Asthma Preventer Prescriptions for School-Age Children During Summer Holiday: TRAINS. *The Asthma UK Centre for Applied Research (AUKCAR) Annual Scientific Meeting 2023.* 24-25 April 2023, Swansea, UK.

Poster Presentations

Alyami R, Julious S, Simpson R, Oliver P. TRial to Assess Implementation of New research in a primary care Setting (TRAINS): study protocol for a pragmatic cluster randomised controlled trial of an educational intervention to promote asthma prescription uptake in General Practitioner Practices. *The Primary Care Respiratory Society (PCRS) Respiratory Conference 2022*. 22–24 September 2022, Telford, UK.

Alyami R, Julious S, Simpson R, Oliver P. TRial to Assess Implementation of New research in a primary care Setting (TRAINS): study protocol for a pragmatic cluster randomised controlled trial of an educational intervention to promote asthma prescription uptake in General Practitioner Practices. *The Asthma UK Centre for Applied Research (AUKCAR) Annual Scientific Meeting 2022.* 15-16 June 2022, Leeds, UK.

Alyami R, Julious S, Simpson R, Oliver P. Can Informing General Practitioners About the Results of Previously Published Research Improve Outcomes in School-Age Children with Asthma. *The Asthma UK Centre for Applied Research (AUKCAR) Annual Scientific Meeting 2020.* 4 May 2020, virtual meeting.

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List of Abbreviations

ACT	Asthma Control Test
AMC	All Medical Contact
CIs	Confidence Intervals
CPRD	Clinical Practice Research Datalink
cRCT	Cluster Randomised Controlled Trial
DMT	Data Management Team
EIA	Exercise-induced Asthma
EPOC	Effective Practice and Organisation of Care
GBD	Global Burden of Disease
GINA	Global Initiative for Asthma
GP	General Practitioner
GPs	General Practitioner practices
HBM	Health Belief Model
ICS	Inhaled corticosteroids
IMD	Index of Multiple Deprivation
IRR	Incident Rate Ratio (IRR)
ISAC	Independent Scientific Advisory Committee
KT	Knowledge Translation
LABAs	Long-acting beta-agonists
LTRAs	Leukotriene receptor antagonists
NHS	National Health Service
NSAIDs	Non-steroidal anti-inflammatory drugs
OCS	Oral corticosteroids
OR	Odds ratios
PEMs	Printed Educational Materials

PLEASANT	Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term
PRR	Prescription Refill Rate
RCT	Randomised controlled trial
RSV	Respiratory syncytial virus
RV	Rhinovirus
SABAs	Short-acting beta-agonists
SMS	Short Message Service
TPB	Theory of Planned Behaviour
UMC	Unscheduled Medical Contact

Chapter 1: Introduction

1.1 Background

Asthma is a chronic condition that affects millions of people worldwide and presents significant challenges in terms of medical care and social impact (WHO, 2022). It is the most prevalent chronic disease in children, with a higher occurrence in the UK compared to other parts of Europe (Valovirta, 2011). Poorly controlled asthma can be a significant burden on affected individuals, their families and society as a whole (Pedersen *et al.*, 2011; Nunes, Pereira and Morais-Almeida, 2017). In the UK, about 1 in 11 children have asthma, highlighting the extent of this public health concern (Asthma UK, 2016).

Asthma has been observed to exhibit a seasonal pattern, with variations in exacerbations and mortality rates influenced by the time of year (Johnston *et al.*, 2005; Sears and Johnston, 2007; Larsen *et al.*, 2016). In England and Scotland, research has shown a marked increase in unscheduled healthcare visits for school-aged children with asthma upon their return to school in September (Julious, Osman and Jiwa, 2007; Julious *et al.*, 2011). This surge may be linked to the inconsistent use of preventer asthma medications during the summer holidays (Julious *et al.*, 2011). This seasonal trend poses a significant challenge for healthcare professionals, children and their parents, emphasising the

importance of maintaining effective asthma management and adherence to prescribed treatments, even during school breaks.

The PLEASANT study (Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term) (Horspool *et al.*, 2013), a cluster randomised controlled trial involving over 12,000 school-aged children across England and Wales, sought to address this challenge. The trial assessed the impact of a simple, doctor-sent letter to parents emphasising the importance of maintaining regular asthma preventer medication use during the summer holidays. The results showed an encouraging 30% increase in prescriptions in August and a subsequent reduction in medical contacts from September to December. Moreover, an estimated cost-saving of £36.07 per patient over the year was reported (Julious *et al.*, 2018).

The PLEASANT trial showed that a simple, cost-effective intervention could increase preventer prescriptions and reduce unscheduled primary care contacts. There is, thus, a clear clinical benefit in translating the results of this clinical research from publication to practice. This leads to the motivation for the TRAINS project.

1.2 Project aim

The success of the PLEASANT study intervention in increasing proscription uptakes in children with asthma paves the way for the TRAINS study—TRial to Assess

Implementation of New research in a primary care Setting. It is important to clarify that despite the use of "implementation" in the title, TRAINS primarily aims to evaluate the impact of informing GPs about these interventions and outcomes, rather than actively implementing the PLEASANT study's interventions within GP practices. The study observes if the dissemination of evidence-based information influences asthma prescription patterns and GP visits among school-aged children during critical periods, such as the summer holidays and the subsequent return to school.

While TRAINS employs the term "implementation" in its designation, it differs from traditional implementation studies in its methodology. Implementation studies are designed to apply and monitor specific interventions within real-world settings to assess their effectiveness and integration into routine practice (Eccles and Mittman, 2006). They often involve a hands-on approach to ensure interventions are carried out as intended and may include elements of training, support, and feedback mechanisms for participants (Eccles and Mittman, 2006). In contrast, TRAINS operates as a Randomised Controlled Trial (RCT) with a specific focus on the observational assessment of how only informing practices about existing research findings influences their behaviours and decisions. This aligns more closely with an evaluation rather than an implementation approach within the spectrum of RCT methodologies (Curran *et al.*, 2012).

This study aims to assess whether informing General Practitioner (GP) practices of the PLEASANT intervention results and study results leads to its implementation (Figure 1.1).

This project will address the following research question:

"Does informing GPs of the results from the PLEASANT trial prevent the drop in prescription uptake in school aged children with asthma during the summer holidays?"

The research question is broken down into several research questions.

1- Does informing GPs about the results of PLEASANT intervention increase preventer prescription uptake in August and September 2021?
2- Will the intervention lead to a decrease in unscheduled or all medical contacts after the return to school from September to December 2021?
3- Will the confirmation of the intervention delivery show any significant findings?
4- Is there any variation in the intervention's impact based on subgroup variables, including sex, age group, and ethnicity?

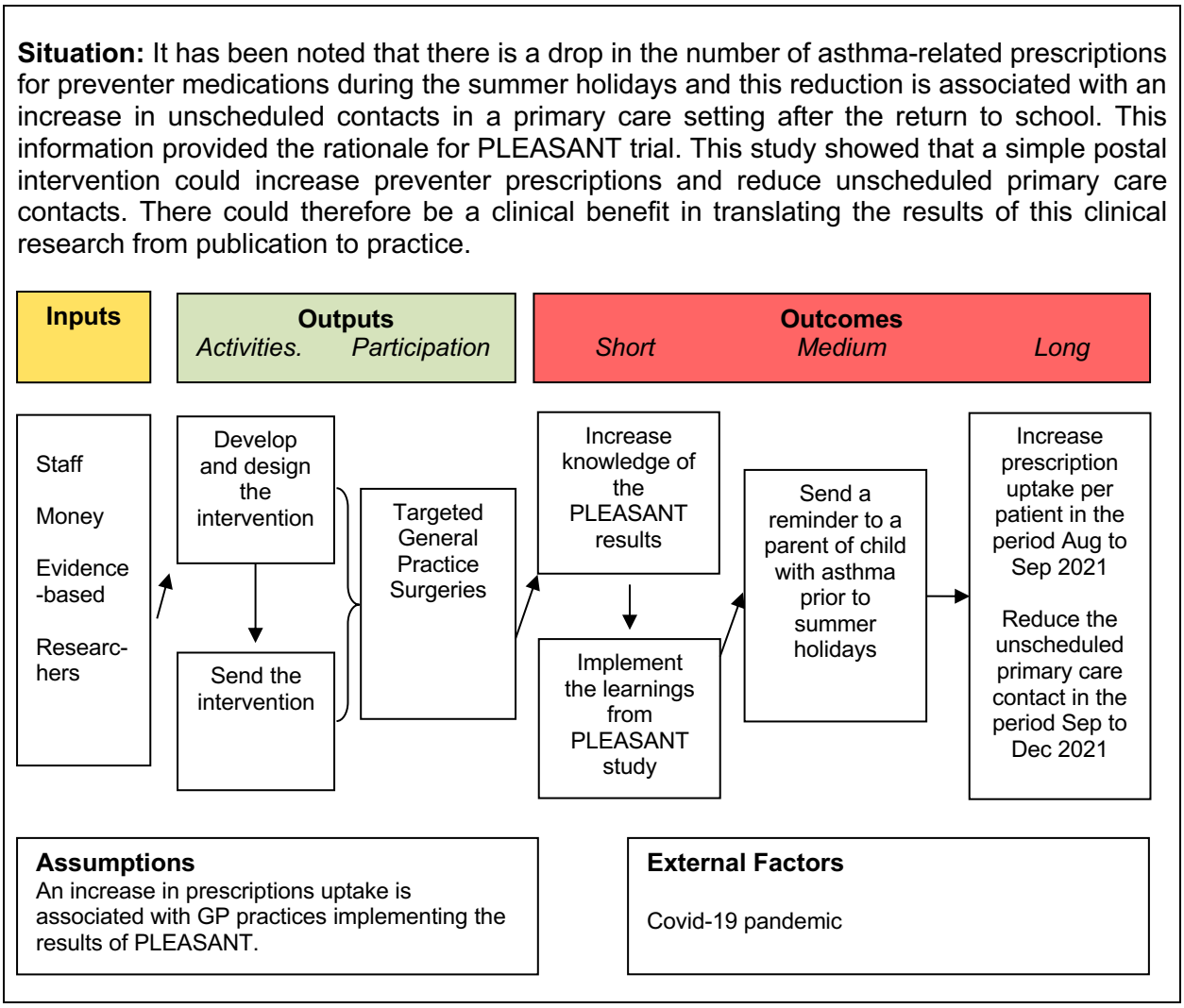


Figure 1-1 A logic model for the TRAINS trial

1.3 Project methods

The current PhD study is a pragmatic cluster randomised parallel-group trial (cRCT) and was conducted in England, involving GP practices contributing to the Clinical Practice Research Datalink (CPRD). This design allows for observing the natural uptake and application of evidence-based recommendations in a real-world setting.

The intervention group received communications from the CPRD, including a letter via postal mail and email, informing them about the PLEASANT study findings and offering recommendations, while the control group received usual care. This method allows for the assessment of whether simply providing GPs with information about PLEASANT trial results in asthma management leads to a measurable change in prescription uptakes. The description of the method is detailed in Chapter 4.

1.4 Outline of thesis

This thesis is organised into seven comprehensive chapters.

Chapter 1 sets the stage for the study by outlining the starting points, aims and the research question of the project.

Chapter 2 provides a background on asthma, its management in children and the seasonal patterns in asthma episodes. It also discusses medication use among school-age children, along with the details of the PLEASANT trial.

Chapter 3 includes a systematic review of printed educational materials as a tool for change, with a focus on letter-based interventions influencing prescription uptake in primary care settings.

Chapter 4 the design of the intervention implemented in this project is thoroughly described.

Chapter 5 refers to the methodology of the project, covering aspects such as study design, outcome measures, data collection techniques and the statistical methods used.

Chapter 6 presents the results of the TRAINS study, alongside sensitivity and subgroup analyses.

Finally, Chapter 7 serves as a discussion chapter. It explores the key findings of the thesis and relates them to the existing literature. It also evaluates the strengths and limitations of the study and provides conclusions and recommendations based on the research findings.

Chapter 2: Background of Asthma and PLEASANT Trial

2.1 Introduction to the chapter

This chapter provides background on asthma, including its definition, prevalence, symptoms, risk factors, triggers, impact on patient's lives, diagnosis and management including ways to improve the quality of life for patients with asthma. Additionally, we will explore the seasonal patterns in asthma episodes and medication use among school-age children. Finally, we will introduce the PLEASANT trial, a study aimed at improving asthma prescription uptake in school-age children during summer holiday.

2.2 Chapter aims

The aims of this chapters are:

- Provide a comprehensive understanding of asthma.
- Explore and describe seasonal asthma in children.
- Provide a summary about the PLEASANT study.
- To contextualise work in context with this PhD

2.3 Definition of asthma

The term “asthma” derives from the Greek word “aazein” which means panting or exhaling with an open mouth (Marketos and Eftychiades, 1986). It was first used as a medical term in the Corpus Hippocraticum (460–370 BC), indicating difficulty in breathing and describing symptoms more severe than dyspnoea (difficult breathing) but less severe than orthopnoea (shortness of breath that occurs when lying flat) (Keeney, 1964). Nowadays, the word "asthma" refers to a specific chronic respiratory disease (Marketos and Eftychiades, 1986). Asthma is chronic inflammatory, non-communicable disease, that targets the airways and can affect individuals of all ages, including children and adults (Vos *et al.*, 2012; NHS, 2021a; WHO, 2022).

According to the Global Strategy for Asthma Management and Prevention 2022 guidelines from the Global Initiative for Asthma (GINA), asthma is defined as follows:
“Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable airflow limitation.”(GINA, 2022).

2.4 Epidemiology

2.4.1 Prevalence

Asthma prevalence refers to the proportion of individuals (or a subgroup of people) with asthma at a particular point of time. This typically requires a review of symptoms over a period, such as the past 12 months, since people with asthma experience intermittent symptoms that may not be present on the day of study (Asher *et al.*, 2020).

As of 2019, the Global Burden of Disease (GBD) estimated that 262 million people worldwide were affected by asthma, with considerable variation in prevalence across different countries (Vos *et al.*, 2020). Asthma is the most common chronic disorder in children (WHO, 2022). According to the Global Initiative for Asthma (GINA), asthma affects 1% to 18% of the global population (GINA, 2022). However, asthma prevalence also depends on how asthma is defined.

In the UK, about 12% of the population, or over 8 million people, have been diagnosed with asthma (Figure 2.1), though some children may have outgrown the condition (BLF, 2019). Asthma UK facts and statistics show that approximately 5.4 million people in the United Kingdom, including 4.3 million adults (1 in 12) and 1.1 million children (1 in 11), are receiving treatment for asthma (Asthma UK, 2016). NHS Digital data indicates that

during the 2020/2021 period, 6.38% of patients aged 6 and older, out of a total of 3,629,070 registered with GPs in England, were diagnosed with asthma (NHS Digital, 2021).

The prevalence of wheezing, one of the most common symptoms in preschool children (defined as aged 1-5 years), is a significant public health issue. A recent cohort study carried out in the UK reported an 8% prevalence rate of wheezing among preschool children in 2017. Moreover, it was found that 35.5% of these children later developed asthma between the ages of 5 and 8 (Chloe I. Bloom *et al.*, 2021).

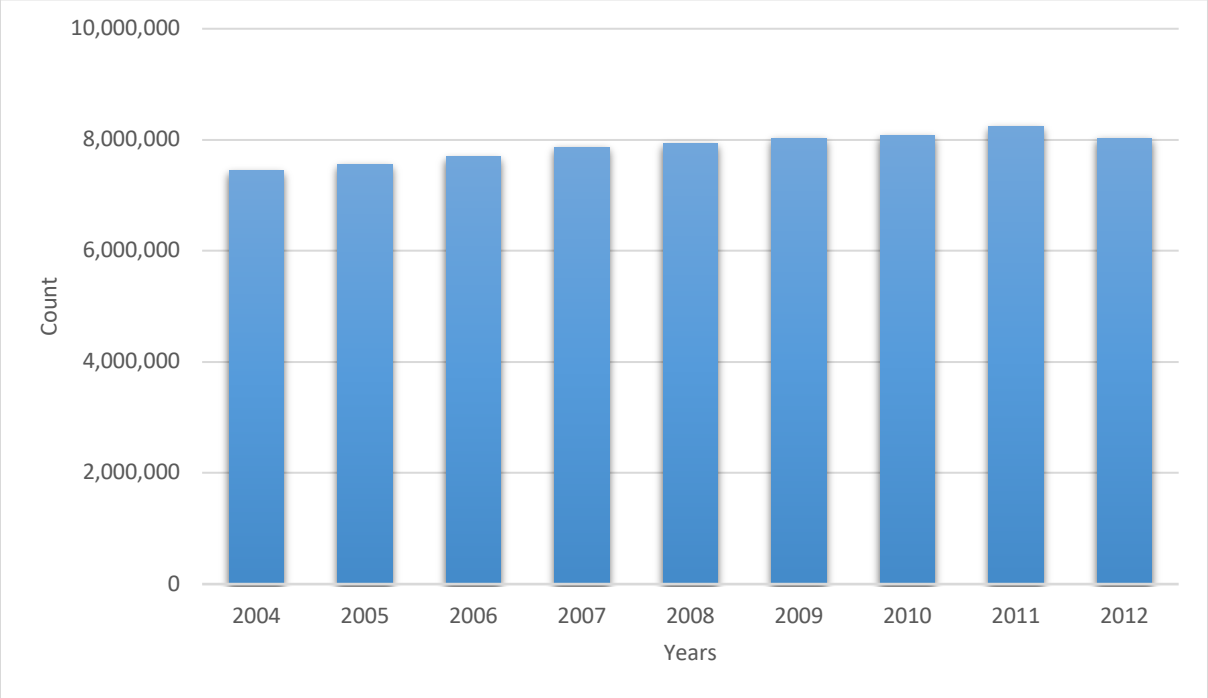


Figure 2-1 Estimated numbers of people ever diagnosed with asthma 2004–2012

The prevalence of children with asthma in the UK is among the highest in Europe (Gibson *et al.*, 2013). In childhood, the prevalence of asthma is greater in boys compared to girls. However, a shift occurs during puberty, resulting in a prevalence that is approximately

20% higher in women than in men (Leynaert *et al.*, 2012). The higher prevalence among boys is partly due to their smaller airways relative to their lung size compared to girls. When children reach puberty, their symptoms tend to diminish or even disappear altogether, especially for those with mild asthma. However, symptoms may persist in children with severe asthma or return in early adulthood (Gerritsen, 2002). Asthma most commonly develops during childhood, but it can also emerge in adulthood (Andersson *et al.*, 2013).

2.4.2 Hospital admission

Hospital admissions for asthma in the UK remain significant, particularly in paediatric populations (Mukherjee *et al.*, 2022). In the 2021-2022 period, the NHS in England reported over 58,000 asthma-related hospital admissions, of which around 49,000 were emergencies. Among these admissions, over 18,000 cases were children aged 16 or younger, with the majority being in the 5-9 year age group, which had over 8,100 visits. Collectively, these patients spent over 660,000 days in hospital beds, highlighting the significant impact asthma has on the NHS (NHS Digital, 2021). It is clear that better asthma management, particularly in younger age groups, is needed to reduce the burden on healthcare resources (Mukherjee *et al.*, 2022).

2.4.3 Socio-economic cost of childhood asthma

Asthma is a long-term condition that can vary in severity throughout a patient's life, causing significant social and economic burdens. It can restrict the physical and social aspects of daily life for children and their caregivers particularly if symptoms are not well-controlled (GINA, 2022). The cost of asthma worldwide is high and differs between countries due to factors like healthcare systems, available resources and how data is collected (Nunes, Pereira and Morais-Almeida, 2017). The costs associated with childhood asthma are multifaceted and can be broadly categorized into direct and indirect costs (Ferrante and La Grutta, 2018).

Direct costs are those related to healthcare utilisation, including hospital admissions, emergency department visits, outpatient visits, medications and other medical services. In the UK, asthma-related costs exceed £1.1 billion annually, with primary care accounting for 74% and hospital care along with disability claims comprising the remaining 25% (Mukherjee *et al.*, 2016).

Indirect costs, on the other hand, are related to productivity losses due to missed school days, parents' time off work to care for sick children and reduced future earning potential for children with severe asthma. Asthma has a significant impact on the health of children in the UK, leading to an average of 252.4 days of school absenteeism per 1,000 children (n/N = 1267/5352), which is equivalent to 2.8 million missed school days (95% CI, 2.6–3.0

million) (Mukherjee *et al.*, 2016), often requiring parents or caregivers to take time off work (Bahadori *et al.*, 2009).

2.5 Pathophysiology of asthma

Asthma is characterised by chronic inflammation and structural changes in the airways (GINA, 2022). A number of factors, such as allergens, infections, obesity, hormonal fluctuations, tobacco smoke, exercise, cold air, genetic mutations and systemic eosinophilia, are known to trigger chronic inflammation in the airways (Turner *et al.*, 2022; WHO, 2022). This inflammation often results in airway obstruction, airway oedema, air hypersensitivity (AHR) and airway remodelling. (NAEPP, 2007).

Bronchoconstriction is the primary physiological event causing asthma symptoms, where the airways narrow due to bronchial smooth muscle contraction. AHR is an exaggerated bronchoconstrictor response to a variety of stimuli. As inflammation becomes more severe and persistent can cause oedema (swelling) in the airways, excessive mucus production and airway remodelling (WHO, 2022). Airway structural changes or remodelling also play a role in the pathophysiology of asthma. Remodelling can include thickening of the airway wall, increased mucus production and increase of the airway smooth muscle. These changes lead to permanent structural alterations in the airways (Holgate, 2008; Bush, 2019).

While the general pathophysiology of asthma is similar in adults and children, there are some differences worth noting. For instance, in many children with asthma, symptoms are triggered by viral infections, particularly rhinovirus. The immune response to these infections can differ between children with and without asthma, suggesting a unique aspect of asthma pathophysiology in children (Holgate, 2008; Bush, 2019).

In addition, the role of allergy in asthma is more prominent in children than in adults. Many children with asthma are sensitized to common aeroallergens and exposure to these allergens can lead to exacerbations of asthma. Moreover, early life events such as exposure to tobacco smoke, viral infections and certain allergens can impact the development and severity of asthma in children (Gans and Gavrilova, 2020). This results in episodes of asthma symptoms such as wheezing, which is most common feature of asthma (GINA, 2022).

2.6 Symptoms of asthma

The symptoms of asthma are not specific and include cough, shortness of breath, wheezing and chest tightness (NICE, 2017; BTS/SIGN, 2019). These symptoms are intermittent and often worsen during exercise or at night. They can occur randomly or in response to certain triggers (NHS, 2021a; WHO, 2022). These triggers, unique to each individual, are influenced by their personal health history. Common triggers may include upper respiratory tract infections, exercise, inhalation of certain chemicals like cigarette

smoke, or allergens such as cat dander or pollen (Turner et al., 2022; WHO, 2022). We will discuss the triggers later in the chapter.

Most asthma characteristic features can be linked to the pattern of symptoms, including the nature of the symptoms, the timing of the symptoms, the triggers and the response to treatment (Papi *et al.*, 2018). Symptoms can range from mild to severe. Most people will only experience occasional symptoms, although a few people may experience symptoms persistently (Holgate *et al.*, 2015).

Asthma symptoms in children may become more apparent during or after physical activity, or they can be triggered by exposure to allergens, infections, or changes in weather (Papi *et al.*, 2018). Night-time coughing and wheezing may disturb sleep, leading to daytime fatigue and issues with concentration at school. In some cases, children may also exhibit signs of "retractions," where the skin between the ribs or the neck sinks in with each breath, indicating difficulty in breathing (van Aalderen, 2012).

It is important to remember that these symptoms can vary greatly between individuals and even within the same individual at different times, which can sometimes make asthma challenging to diagnose in children (NAEPP, 2007; BTS/SIGN, 2019).

2.7 Asthma exacerbations

Asthma's natural progression is often punctuated by acute or subacute periods of intensified symptoms, commonly known as exacerbations, asthma attacks, or flare-ups, requiring treatment change (Papi *et al.*, 2018). These episodes are marked by a progressive increase in shortness of breath, coughing, wheezing, chest tightness and a decline in lung function. In children, the onset of these symptoms is usually rapid, while in adults, it can take a week or more to develop (Papi *et al.*, 2018).

Exacerbations contribute significantly to asthma-related cost and can have a detrimental impact on the quality of life of patients (Dunican and Fahy, 2015). They can also be fatal in some cases, including patients with mild asthma (Dusser *et al.*, 2007) with more than 25,000 children admitted annually with asthma attacks (Levy, 2015).

Both in adults and children, the inappropriate use of asthma medications, specifically poor adherence to inhaled corticosteroids and over-reliance on short-acting β2 agonists, is correlated with a heightened risk of severe asthma exacerbations and fatalities. Alarmingly, one person experiences a life-threatening asthma exacerbation every ten seconds in the UK and on average, three people die from asthma daily (Asthma UK, 2016). Despite this, there has been a noted decrease in asthma-related deaths (Vos *et al.*, 2012), potentially due to the increased use of asthma control medications (Papi *et al.*, 2018).

2.8 Diagnosis

Diagnosing asthma presents a challenge due to the absence of a definitive gold standard (NICE, 2017). The approach to diagnosis typically relies on evaluating the likelihood of asthma based on symptoms and the severity of airflow limitation during exhalation, known as expiratory airflow (Education and Program, 2007; Quirt *et al.*, 2018). However, each patient may manifest distinct signs and symptoms, which can complicate the diagnostic process (Holgate *et al.*, 2015).

A diagnosis of asthma in children aged five and under can be particularly challenging, given that episodic symptoms such as breathlessness, cough and wheezing often coincide with common colds. Consequently, a diagnosis is often established through a comprehensive clinical assessment, which heavily depends on parents' accounts of these symptoms (Pedersen *et al.*, 2011; Danvers, Lo and Gaillard, 2020). Between 2007 and 2017, there was a significant decline in the number of preschool children with wheezing who were diagnosed with asthma across all age groups. In 2007, over one-third of children aged 4 to 5 years received an asthma diagnosis. However, by 2017, this proportion decreased to approximately one-fifth. Moreover, in 2017, less than 5% of children aged 1 to 2 years with wheezing were diagnosed with asthma. This could be due to an increasing hesitation to label preschool children who wheeze as asthmatic. The likelihood of

receiving an asthma diagnosis increased as the child grew older. (Chloe I. Bloom *et al.*, 2021).

In the UK, there exist two primary national guidelines providing treatment recommendations for asthma. These guidelines, developed by the British Thoracic Society in partnership with the Scottish Intercollegiate Guidelines Network (BTS/SIGN) and by the National Institute for Health and Care Excellence (NICE), aim to advise on the optimal approaches for managing and diagnosing asthma (NICE, 2017; BTS/SIGN, 2019; Drake, Simpson and Fowler, 2019).

According to the NICE guidelines, relying solely on clinical assessment for asthma diagnosis has poor specificity and may lead to over-diagnosis. Therefore, objective investigations are recommended for asthma diagnosis (see Fig 2.2). NICE recommends using an algorithm with sequential tests, including airflow obstruction such as spirometry, airflow variability, bronchodilator reversibility (BDR), airway inflammation (i.e. fractional exhaled nitric oxide (FeNO)) and bronchial challenge tests if necessary. Asthma diagnosis relies on medical history, physical examination and lung function tests for accurate assessment (NICE, 2017).

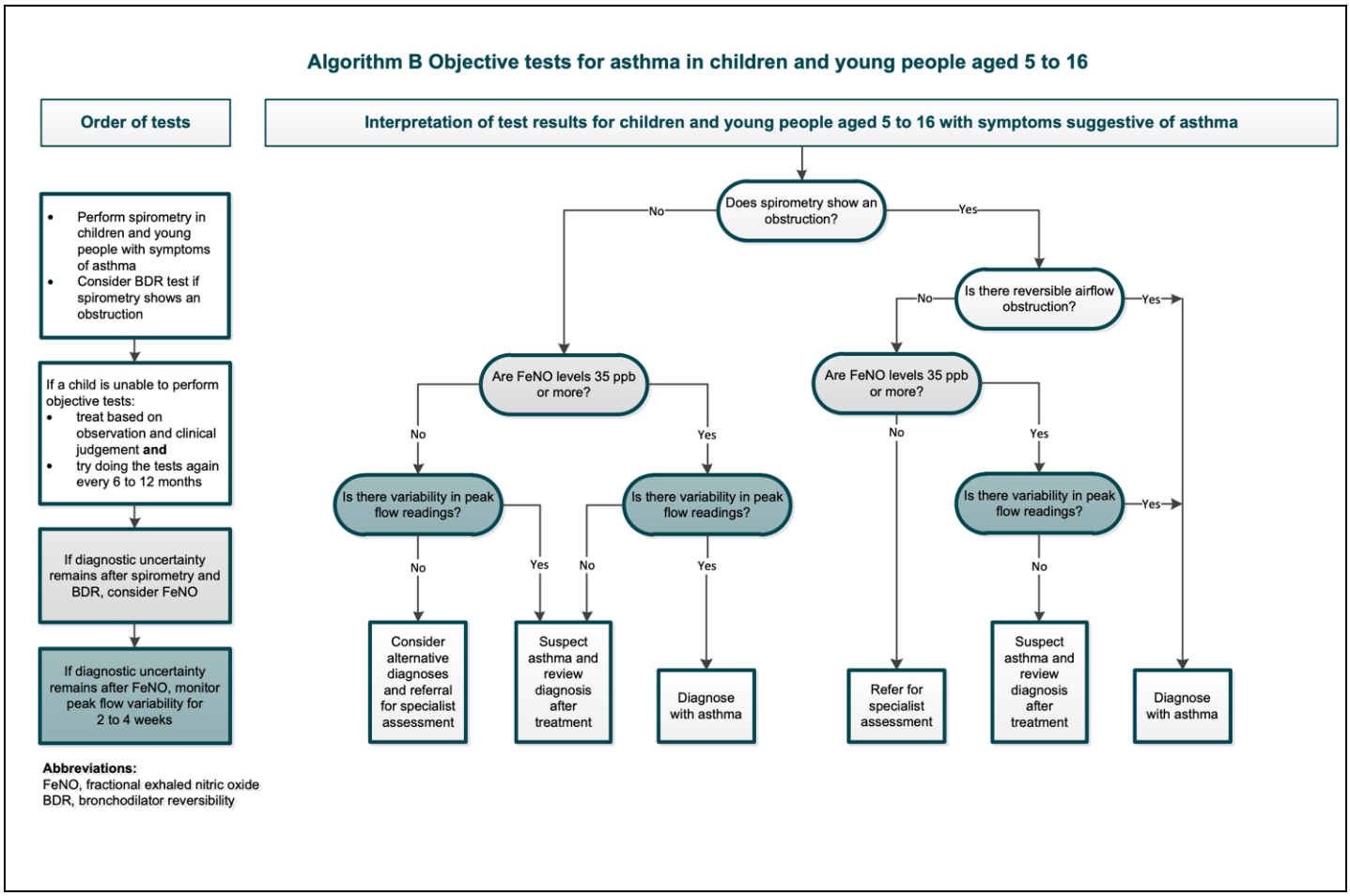


Figure 2-2 NICE diagnostic algorithm in children (NICE, 2017)

2.9 Risk factors for asthma

There is no exact cause of asthma (NHS, 2021a). However, there are a number of factors that can lead to the development of asthma, including environmental factors (pollens, air pollution, weather and other aeroallergens), genetic factors (asthma susceptibility loci on genes) and host factors (allergic sensitisation, obesity, infections and nutritional factors) (WHO, 2022).

Asthma onset in childhood and adulthood share many of the same causes and triggers. Although the evidence mainly supports environmental factors as triggers rather than causes of asthma, there is also growing evidence that interrelationships between environmental factors and other intrinsic factors, including genetics and atopy, may possibly contribute to asthma development (Dharmage, Perret and Custovic, 2019). Typically, childhood asthma manifests as an allergic phenotype, whereas adult-onset asthma is characterised by a predominantly non-allergic phenotype (Romanet-Manent *et al.*, 2002). In the next section, we discuss the triggers in more detail.

2.10 Triggers of asthma

Asthma triggers are stimulants, conditions, or substances that can start asthma symptoms. Triggers lead to inflammation of the airways and result in an asthma exacerbation (Asthma UK, 2022). In children, viral infections are the main trigger of asthma (Gautier and Charpin, 2017). In routine asthma care, specific asthma triggers should be identified and documented. It is important to learn how to recognise triggers and avoid them (Martin, Townshend and Brodlie, 2022).

2.10.1 Viral respiratory infections and seasonality

The majority of asthma exacerbations in children (more than 80%) are caused by viral infections (Busse, Lemanske and Gern, 2010). Rhinovirus (RV) and respiratory syncytial

virus (RSV) are both associated with wheezing episodes in early childhood and the risk of recurrence of wheezing (Jackson *et al.*, 2008). During September, rhinovirus infections are sometimes known as the "September epidemic", due to the high frequency of children with asthma presenting to emergency departments with exacerbations (Johnston *et al.*, 2005).

In addition to RV and RSV, other viruses have also been involved to cause respiratory illness, including enterovirus, coronavirus and human metapneumovirus. A virus can interact with allergens to cause asthma exacerbations and may also result in hospitalisation (Murray *et al.*, 2006).

The only preventive measures that are available are keeping away from infected subjects, preventer inhaler adherence, immunisation against the flu and pharmacological treatment during the first few days following contamination by the virus (Gautier and Charpin, 2017).

2.10.2 Air pollution

Air pollution has a signifiant effect on asthma in both children and adults worldwide (Anenberg *et al.*, 2018). People living in populated cities have a higher risk of developing asthma (Subbarao, et al, 2009). It has been demonstrated that, in a natural experiment conducted on 60 young to middle-aged adults with mild to moderate asthma, walking along Oxford Street was associated with reduced lung function, neutrophilic

inflammation and airway acidification, when compared with walking in the less polluted Hyde Park in London (McCreanor *et al.*, 2007). Individuals with moderate asthma at baseline experienced greater changes than those with mild asthma.

For more than two decades, asthma prevalence and mortality have been shown to be increased in children living in cities compared to non-urban children. In addition, more recent studies show that indoor pollutants is higher than outdoor pollutants in many countries such U.S. and Europe and exposure to indoor pollutants like nitrogen dioxide and particulate matter are associated in children with asthma (Togias *et al.*, 2010).

2.10.3 Tobacco smoke

Tobacco smoke exposure is known to be a powerful trigger for athsma which irritates airways. Tobacco smoke exposure includes parental smoking, other secondhand smoke exposue and personal smoking (Burke *et al.*, 2012; Toskala and Kennedy, 2015). It has also been shown in several epidemiological studies that parental smoking is strongly correlated with preschool wheezing and the development of asthma in children (Strachan and Cook, 1998; Lannerö *et al.*, 2006; Accordini *et al.*, 2012; Burke *et al.*, 2012). In addition, children who have been exposed to secondhand smoke tend to smoke later in life and are at increased risk of developing chronic obstructive pulmonary disease (COPD) (Goksör *et al.*, 2007).

2.10.4 Pollen

Pollen is a major trigger of asthma exacerbations in children requiring emergency department visits and has been linked to seasonal asthma (Erbas *et al.*, 2018). Patients with asthma often experience hay fever (Allergic rhinitis) as a result of exposure to pollen (Bousquet *et al.*, 2008). Changes in weather such as, rain and humidity may induce hydration of pollen grains, as well as fragmentation, resulting in the generation of aerosols with allergens in the atmosphere. During the first phase of a thunderstorm, those who suffer from allergic rhinitis may inhale high concentrations of allergenic material dispersed in the atmosphere, which may result in asthmatic symptoms, sometimes even severe symptoms (Bousquet *et al.*, 2008; Erbas *et al.*, 2018).

2.10.5 Excercise

Exercise-induced Asthma (EIA) is a common trigger of asthma symptoms, especially in children with asthma (Randolph, 2008). It was found that up to 90% of children with persistent asthma experience EIA (Weiss, 2011). EIA is a condition that occurs during or after strenuous physical activity causes narrowing of the airways in the lungs, resulting in shortness of breath, coughing and wheezing (Klain *et al.*, 2022). The causes of EIA are not fully understood, but several theories have been proposed (Weiss, 2011).

One theory is that exposure to cold dry air may be a trigger for EIA. During exercise, the body requires a greater amount of oxygen, resulting in faster, deeper breathing through

the mouth. The air that enters the lung from the mouth is dryer and cooler than when it enters through the nose, which lead the airways to to dry out (dehydration), leading to inflammation and bronchoconstriction (Randolph, 2008; Parsons *et al.*, 2013).

Up to 23% of school-aged children suffer from EIA, which negatively affects the quality of their lives (Anderson, 2002; Merikallio *et al.*, 2005). In addition, a study found that 79% of children experience EIA as the most burdensome aspect of their asthma, that limits participation in sports and other activities (Vahlkvist, Inman and Pedersen, 2010).

EIA is diagnosed by performing a lung function test called a bronchoprovocation test, in which a person exercises and then lung function is measured before and after exercise (Weiss, 2011; Parsons *et al.*, 2013; Holgate *et al.*, 2015). Treatment for EIA typically includes inhaled bronchodilators, which help to open the airways and inhaled corticosteroids, which help to reduce inflammation. Also, nonpharmacologic treatment involves a number of maneuvers that are effective in reducing EIA such as warm-up exercises, cooling down slowly after exercise, use of face masks in cold weather and breathing predominantly through the nose instead of the mouth during exercise (Randolph, 2008; Weiss, 2011; Parsons *et al.*, 2013; Klain *et al.*, 2022).

2.10.6 Medications

It has been acknowledged that some medications may cause asthma symptoms to worsen in some patients with asthma. There are two groups of drugs that are often linked to

worsening asthma symptoms, they are non-steroidal anti-inflammatory drugs (NSAIDs), which include ibuprofen and aspirin and beta-blockers (Holgate et al., 2015; NICE, 2017; Kercsmar and Mcdowell, 2019).

Studies show that less than 10% of asthma patients experience worsening of respiratory symptoms after taking NSAIDs (Vally, Taylor and Thompson, 2002). The exacerbation of asthma symptoms due to NSAIDs and aspirin is understood to be related to a shift in arachidonic acid metabolism from the cyclooxygenase pathway to the 5-lipoxygenase pathway, leading to an increased production of leukotrienes. These leukotrienes are powerful bronchoconstrictors and contribute to inflammatory processes in the airways, particularly in individuals with aspirin-exacerbated respiratory disease (AERD) (Stevenson, 1998; Rees, Kanabar and Pattani, 2013). Respiratory disease caused by aspirin use is more prevalent in individuals with severe asthma, affecting 15% of those with severe asthma compared to 7% in the general population (Rajan *et al.*, 2015). It is often preceded by symptoms of rhinitis and nasal polyposis, however, it is uncommon in children (Jenkins, Costello and Hodge, 2004).

A cohort study in Taiwan was conducted to assess the correlation between aspirin/NSAIDs and the possibility of asthma worsening in children with asthma. It found that short-term use of aspirin, ibuprofen and diclofenac may be linked to an increase in asthma symptoms in children with asthma. However, no correlation was

found between long-term use of these medications and the risk of asthma exacerbation (Lo *et al.*, 2016). The exact reason for this exacerbation is unknown but thought to be related to the drugs' impact on the metabolism of inflammatory mediators, such as leukotrienes (NICE, 2017).

Regarding beta-blockers, their use in asthma patients, especially in children, is approached with caution (Holgate *et al.*, 2015). Beta-blockers can worsen asthma symptoms by increasing airway resistance due to their effect on blocking beta-2 adrenergic receptors, which are responsible for bronchodilation (Covar, Macomber and Szefler, 2005; Morales *et al.*, 2014). While their use in children with asthma is generally avoided, there might be specific cases, such as severe cardiovascular diseases, where the benefits of beta-blockers could outweigh the risks. Close monitoring of respiratory status is essential in these scenarios (Morales *et al.*, 2014).

2.10.7 Psychological factors

Psychological or Emotional factors, such as stress and anxiety, can trigger asthma symptoms and a higher risk of asthma exacerbations (Gautier and Charpin, 2017; NICE, 2017; Landeo-Gutierrez et al., 2020). Research over the past decade has shown that stress and stress-related factors experienced during pregnancy and early childhood (such as maternal anxiety or depression) can increase the risk of respiratory disorders in children (Rosa, Lee and Wright, 2018).

Besides triggering asthma symptoms, stress and emotional factors at home and work can contribute to poor asthma control and decreased medication compliance. When a person is feeling stressed or emotional, they may not be able to focus on their medication plan or remember to take their medication at the right times (Landeo-Gutierrez *et al.*, 2020).

Coping styles of patients, their families and doctors can affect the severity of asthma and denial of the condition by any of these parties can delay treatment. Psychological factors have been linked to deaths from asthma in children and psychosocial factors can also affect compliance with treatment (Kercsmar and Mcdowell, 2019). Asthma can also affect the emotional state of patients, their families and others associated with them. Studies also suggest that psychosocial stressors can modulate immune responses, increase inflammation and decrease steroid responsiveness, leading to poorer asthma control (Brehm *et al.*, 2015; Verkleij *et al.*, 2015). It was found in another study that anxiety can worsen the impact of poor sleep on childhood asthma control (Daniel *et al.*, 2012).

Children with asthma may be influenced by psychological factors and its severity may be affected by family issues. A systematic review in the Cochrane Database discovered only two studies on interventions and suggested that family therapy, in addition to medication, may be beneficial for children with asthma (Yorke and Shuldham, 2005).

2.11 Effects of asthma on quality of life

Asthma is a condition that can significantly impact individuals' lives in various ways (Anderson *et al.*, 2007). It may limit people's activities and prevent them from participating in physical activities (Newacheck and Halfon, 2000).

Furthermore, asthma can reduce a child's quality of life. Children with asthma and their families may suffer physical, emotional and social limitations as a result of asthma (Kalyva, Eiser and Papathanasiou, 2016). School-age children with asthma may miss school and they are may be unable to participate in sports (Moonie *et al.*, 2006). In addition, it can affect the academic performance of children which may be attributed to absenteeism due to the disorder and inability to perform normal activities (Moonie *et al.*, 2006).

Asthma has been identified as the leading cause of disability among individuals under the age of 18 years. Over the past 25 years, asthma has led to increasing rate of disability among children and adolescents. The risk of disability is increased three times among children diagnosed with asthma (Newacheck and Halfon, 1998).

Asthma can also affect the mental health of patients, with a higher risk of depression and isolation among those suffering from asthma. Uncontrolled asthma symptoms can cause people to isolate themselves, disrupting normal activities and causing mental health

issues such as stress, isolation and depression (Goodwin *et al.*, 2012). A Washington Healthy Youth survey was conducted between 2010 and 2012 found that nearly 32% of children with asthma suffered from depression, while 19% reported having suicidal thoughts (State, 2013). Controlling and managing asthma effectively can lead to an improved quality of life for people (Education and Program, 2007).

2.12 Management of asthma

Asthma management aims to control the disease and prevent exacerbations, reducing the risk of morbidity and mortality (Education and Program, 2007). It also aims to minimise the severity and frequency of asthma symptoms, decreasing the need for reliever medications and normalising physical activity while improving lung function and the quality of life (Quirt *et al.*, 2018). In the UK, the National Institute for Health and Care Excellence (NICE) provides guidelines for the treatment of asthma in both adults and children (NICE, 2017). The British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) also collaborate to produce a comprehensive guideline, which is updated regularly (BTS/SIGN, 2019) .

2.12.1 Asthma Assessment

The goal of managing asthma in both children and adults is to reduce the impact of symptoms on daily life, sleep and physical activity while also minimising the risk of

adverse outcomes. These outcomes include exacerbations, persistent airflow limitation and medication side effects. It is essential to maintain control over asthma symptoms to achieve these goals (NICE, 2017; Papi *et al.*, 2018; BTS/SIGN, 2019; GINA, 2022).

Healthcare providers often use tools like the Asthma Control Test for adults or children to monitor and evaluate asthma symptom control. However, it is vital to understand that monitoring symptoms is only a part of the comprehensive management of asthma. Uncontrolled symptoms do indeed increase the risk of exacerbations, but the presence of other significant risk predictors remains important regardless of symptom control (Schatz *et al.*, 2006; Liu *et al.*, 2007). In children, these factors include the overuse of short-acting β2 agonists and failure to properly receive inhaled corticosteroids due to reasons such as not being prescribed these medications, incorrect inhaler technique, or poor adherence to medications. Additional factors contributing to increased asthma risk as we mentioned before include exposure to allergens, food allergies, upper respiratory viral infections (particularly when also exposed to allergens), as well as psychological and socioeconomic issues and problems at home or school (Papi *et al.*, 2018). To minimise risk factors and comorbidities, it is recommended to review them at least once a year (BTS/SIGN, 2019).

2.12.2 Pharmacological treatment

Medication treatment of asthma consists of two main categories: preventer medications and reliever medications. Preventer medications are used to provide long-term control of

symptoms and prevent exacerbations, while reliever medications are used to rapidly relieve asthma symptoms and asthma attack (NICE, 2017; BTS/SIGN, 2019; GINA, 2022).

2.12.2.1 Preventer medications

As stated above, preventer medications, also known as asthma controllers, are the foundation of asthma management for individuals with persistent asthma. Their primary goal is to maintain stable asthma control by reducing airway inflammation and preventing the frequency and severity of asthma attacks, and reduce the risk of long-term health problems associated with asthma (Rees, 2010; GINA, 2022). These medications are typically taken daily, regardless of the presence or absence of symptoms (NICE, 2017). There are a wide range of preventer medications available and some of the most common ones are described below.

Inhaled corticosteroids (ICS) ICS serve as foundation of asthma treatment because they effectively reduce airway inflammation and improve asthma control (GINA, 2022). The choice of ICS depends on the individual patient's needs and local prescribing guidelines. Common ICS agents include beclomethasone, budesonide, ciclesonide, mometasone and fluticasone (BTS/SIGN, 2019). These medications are used for long-term prevention of asthma symptoms and to control inflammation. They work by blocking allergic reactions, reducing airway hyperresponsiveness, inhibiting cytokine production, and preventing inflammatory cell migration. Potential side effects include cough, oral thrush, and, at high

doses, systemic effects like adrenal suppression and osteoporosis. Therapeutic considerations involve using spacer devices to decrease local side effects and balancing the risks of uncontrolled asthma against the risks of ICS therapy (NAEPP, 2007; NICE, 2017; GINA, 2022).

Systemic Corticosteroids: This group includes methylprednisolone, prednisolone, and prednisone, used for short-term control of acute asthma and long-term prevention in severe cases, such as refractory asthma (NICE, 2017). They share similar mechanisms with inhaled corticosteroids. Adverse effects can range from glucose metabolism abnormalities and mood changes in the short term to more serious long-term issues like adrenal suppression and cataracts. Their use necessitates careful consideration of coexisting conditions like diabetes and hypertension. It's recommended to use the lowest effective dose and consider alternate-day dosing to minimise toxicity (NAEPP, 2007; GINA, 2022).

Long-acting beta-agonists (LABAs): LABA are always combined to ICS in a single inhaler for patients whose asthma remains uncontrolled with ICS alone (NICE, 2017). LABAs, such as salmeterol and formoterol, provide bronchodilation and help improve symptoms and lung function. These medication can last 12 hours and lower risk of exacerbation (BTS/SIGN, 2019). They work by inducing bronchodilation and smooth muscle relaxation. Side effects can include tachycardia and muscle tremor. LABAs should

not be used as monotherapy but can be effective when added to ICS (NAEPP, 2007; GINA, 2022).

Leukotriene receptor antagonists (LTRAs): This group includes montelukast and Zafirlukast, serve as an alternative add-on treatment for patients who are unable to tolerate LABAs or require additional control. Unlike steroids, montelukast reduces inflammation via a distinct mechanism of action (NICE, 2017). LTRAs used for long-term control and prevention of symptoms in mild to moderate persistent asthma. They work by inhibiting leukotriene receptors. While Montelukast has no specific adverse effects, Zafirlukast has been linked to reversible hepatitis and, in rare cases, hepatic failure. Therapeutic considerations include monitoring liver function and being aware of potential interactions with other medications like warfarin (NAEPP, 2007; GINA, 2022).

Cromolyn Sodium and Nedocromil: These medications are used for long-term prevention of symptoms in mild persistent asthma and work by blocking allergic reactions and stabilizing mast cell membranes. Common side effects include cough and irritation, with some patients experiencing an unpleasant taste from Nedocromil. It may take up to 6 weeks to determine their full benefit, and their safety is a primary advantage (NAEPP, 2007; NICE, 2017; GINA, 2022).

Immunomodulators (Omalizumab/Anti-IgE): Omalizumab is used for long-term control in adults with moderate to severe persistent allergic asthma. It works by binding to circulating IgE and preventing it from binding to receptors on basophils and mast cells.

Side effects include injection site pain and bruising, and there's a small risk of anaphylaxis. It's important to monitor patients post-injection and manage the dosing based on body weight and IgE levels (NAEPP, 2007; NICE, 2017; GINA, 2022).

Methylxanthines (Theophylline): Used for long-term control in mild persistent asthma or as adjunctive therapy with ICS, they work by inducing bronchodilation through phosphodiesterase inhibition. Side effects can range from nausea and tachycardia to seizures at high doses. Therapeutic monitoring of serum concentrations is essential due to its narrow therapeutic range (NAEPP, 2007; NICE, 2017; GINA, 2022).

2.12.2.2 Reliever medications

As previously mentioned, reliever medications, also known as rescue medications, are used to provide quick relief from Asthma symptoms. There are two main types of reliever medications: short-acting beta-agonists (SABAs) and anticholinergic bronchodilators (Asthma UK, 2021). Below are some descriptions of a few types of reliever medication:

Short-acting beta-agonists (SABAs) serve as the primary reliever medications for acute asthma symptoms (NICE, 2017). Salbutamol (albuterol) and terbutaline are two most common of SABAs, which are highly effective in providing rapid bronchodilation and relief from breathlessness, wheezing and chest tightness. While SABAs are essential for providing relief from acute asthma symptom, but it is important to note that they should be prescribed as needed and should not be used as a regular treatment for asthma control

(BTS/SIGN, 2019). Side effects include tachycardia and muscle tremor. The inhaled route is preferred due to fewer systemic effects (NAEPP, 2007; GINA, 2022).

Anticholinergic bronchodilators, like ipratropium bromide, can be used as an adjunct to SABAs in acute severe asthma exacerbations or for those who cannot tolerate SABAs (BTS/SIGN, 2019). Anticholinergic bronchodilators help to relax the airway muscles and improve airflow. These work by inhibiting muscarinic cholinergic receptors and reducing intrinsic vagal tone in the airways. Side effects include dry mouth and respiratory secretions. They are particularly useful for patients intolerant to SABAs and as a choice for bronchospasm due to beta-blocker medication (NAEPP, 2007; GINA, 2022).

2.12.3 Stepwise approach for manage asthma

In asthma management, stepwise treatment is widely accepted as a method that aims for optimal asthma control with the minimum amount of medication required. This approach has five steps, each increasing the intensity of the medication (Rees, 2010; Papi *et al.*, 2018; BTS/SIGN, 2019).

Step 1: SABAs for symptom relief

At this step, patients with intermittent or mild asthma symptoms use a reliever inhaler containing SABAs like salbutamol or terbutaline. SABAs relax the airway's smooth muscles, offering rapid relief from bronchoconstriction. Patients should take their SABA

inhaler as needed. If symptoms persist or worsen, patients progress to Step 2 (Rees, 2010; Papi *et al.*, 2018; BTS/SIGN, 2019).

Step 2: Regular preventer therapy

Step 2 involves preventer medications, typically a low-dose ICS like beclomethasone or fluticasone which will be prescribed to patients. Alternatively, LTRA such as montelukast may be prescribed. Preventer treatments take about two weeks to work and its necessary to be taken every day even if the patient feel well. Patients should continue using their SABA inhaler as needed (Rees, 2010; Papi *et al.*, 2018; BTS/SIGN, 2019).

Step 3: First-line add-on therapy

Step 3 expands the treatment plan to improve asthma control. The most common add-on therapy is LABA like formoterol or salmeterol, combined with the existing ICS. Alternatively, an LTRA may be added if not already prescribed. Patients should continue using their SABA inhaler as needed (Rees, 2010; Papi *et al.*, 2018; BTS/SIGN, 2019).

Step 4: Escalating therapy

If asthma symptoms remain inadequately controlled, treatment intensification is required. This may involve increasing the ICS dose, adding a fourth drug, long-acting muscarinic antagonists (LAMAs) like tiotropium, or theophylline. The LTRA may also be added if not already prescribed. Patients should continue using their SABA inhaler as needed (Rees, 2010; Papi *et al.*, 2018; BTS/SIGN, 2019).

Step 5: Advanced treatment options

At Step 5, patients with severe or refractory asthma may need further intervention, such as continuous or frequent use of oral corticosteroids (OCS) like prednisolone. However, long-term OCS use has significant side effects and should be avoided when possible. Alternatively, biologic therapies such as monoclonal antibodies (e.g., omalizumab, mepolizumab, or benralizumab) may be initiated, targeting specific immune system components involved in inflammation (Rees, 2010; Papi *et al.*, 2018; BTS/SIGN, 2019).

The stepwise approach to asthma management allows for individualised treatment plans, ensuring optimal asthma control with minimal medication. By understanding the five steps, healthcare providers can effectively manage patients' asthma symptoms and improve their quality of life (Rees, 2010; Papi *et al.*, 2018; BTS/SIGN, 2019).

2.12.4 Adherence

Adherence, the extent to which patients follow their healthcare provider's instructions, is fundamental to the effective management of chronic conditions like asthma (Boutopoulou *et al.*, 2018). The challenge of achieving satisfactory adherence is especially critical with inhaled corticosteroids (ICSs), where suboptimal use often leads to poorer asthma control (Bender, Milgrom and Apter, 2003). Patients exhibiting "difficult to control" symptoms due to adherence rates below 60% highlight the significance of consistent medication use in managing asthma effectively (Jochmann *et al.*, 2017). Poor

adherence is associated with increased risks of asthma exacerbations, hospitalisations, asthma-related deaths and worsened lung function (Asthma UK, 2016). Despite the known benefits of adherence to inhaled treatments in improving asthma control and reducing morbidity (Feldman *et al.*, 2012; Klok *et al.*, 2015), adherence levels frequently fall short, resulting in poorer health outcomes and elevated healthcare costs (Normansell, Kew and Stovold, 2017).

The measurement of adherence includes factors like Prescription Refill Rate (PRR), patient behaviours, and healthcare practices. (Bender *et al.*, 2006; Graves, Adams and Portnoy, 2006). PRR measures how frequently patients collect their medication from pharmacies, provides valuable insights into medication usage. However, PRR does not guarantee medication is taken as prescribed, administered correctly, or even if it's used by the intended patient. Sometimes, medication is simply stored away and never used (Hazell and Robson, 2015). The tendency to stockpile medications, as seen during the COVID-19 pandemic, suggests that patients might accumulate medications under various circumstances (Dhruve *et al.*, 2022). Despite PRR's limitations, it remains an important metric for understanding medication use and identifying complete non-adherence like no prescription collected (Gustafson *et al.*, 2012; Julious *et al.*, 2016). Moreover, PRR can give us valuable information about how often salbutamol is used and can indicate when it is being used too much, which can lead to worse asthma outcomes (GINA, 2022).

The PLEASANT study provides valuable insights into medication collection patterns, notably observing increased prescription collections in both August and September. This trend suggests that parents of children with asthma are proactive in managing their children's medication needs, aligning medication collection with anticipated periods of higher demand, such as the return to school—a time associated with an uptick in asthma exacerbations (Julious *et al.*, 2018).

Adherence rates among children to asthma medication are notably variable, with objective measurements indicating 49-71% adherence (Desager, Vermeulen and Bodart, 2018). The fact that only 55% of children with moderate to severe persistent asthma use their controller medication consistently each day highlights the need for enhanced adherence strategies (Diette *et al.*, 2001). Furthermore, more than half of children referred to a specialised care centre for severe asthma have a prescription pick-up rate of less than 80%, indicating poor adherence (Bracken et al., 2009).

A study conducted in East London links higher prescribing ratios with lower hospital admission rates, emphasising the importance of sufficient access to asthma medication for effective management and prevention of severe exacerbations (Griffiths *et al.*, 1996). Additionally, asthma-related mortality risk has been demonstrated to rise as the collection of inhaled corticosteroids (ICS) canisters decreases. Notably, a substantial increase in risk is observed when the annual collection of ICS canisters falls below nine

per year, which corresponds to approximately 70-80% adherence, as indicated in a population-based cohort study (Suissa *et al.*, 2000). Furthermore, a study investigated the relationship between adherence rates to ICS and LTRA (measured through PRR) and healthcare attendances in children. Their findings revealed a significant correlation between lower adherence rates and higher frequencies of healthcare visits, underscoring the importance of improving adherence in patient care management (McNally *et al.*, 2009).

Improving adherence to asthma treatment is crucial for reducing the burden of this condition. Better adherence leads to better control and less severe asthma symptoms (Jentzsch *et al.*, 2012; Klok *et al.*, 2014, 2015). There are various interventions that could help improve adherence, including shared decision-making for medication and dose choices (Wilson *et al.*, 2010), inhaler reminders (Chan *et al.*, 2015), home visits (Otsuki *et al.*, 2009) and prescribing inhaled corticosteroids (ICS) once a day instead of twice (Price *et al.*, 2010).

2.12.5 Monitoring and follow-up

Effective asthma management requires consistent monitoring and follow-up to assess treatment efficacy, identify potential triggers, evaluate inhaler technique and assess adherence to medication. Asthma is a variable condition that can change over time and it

is crucial to adapt the management plan according to these changes. (NICE, 2017; BTS/SIGN, 2019).

Patients should be reviewed regularly to assess their symptoms, impact on daily activities, frequency of exacerbations, lung function and medication use (NICE, 2017; BTS/SIGN, 2019). Healthcare providers commonly use questionnaires such as ACT for adults and children to monitor symptom control. These questionnaires can guide healthcare providers in determining the severity of a patient's asthma and whether adjustments to their treatment plan are necessary (Schatz *et al.*, 2006; Liu *et al.*, 2007).

Healthcare providers should also ensure that patients are using their inhalers correctly as incorrect technique can lead to poor asthma control (BTS/SIGN, 2019). Furthermore, addressing adherence to medication is pivotal as poor adherence can significantly increase the risk of exacerbations and hospital admissions (Klok *et al.*, 2014).

Moreover, the identification and management of triggers are vital in preventing exacerbations. This involves identifying allergens and irritants that can worsen asthma symptoms and providing advice on how to avoid or reduce exposure to these triggers (NICE, 2017; BTS/SIGN, 2019; GINA, 2022).

In summary, monitoring and follow-up are integral components of comprehensive asthma management, aimed at maintaining control over symptoms, reducing the risk of

exacerbations and improving the quality of life for individuals with asthma (NICE, 2017; BTS/SIGN, 2019; GINA, 2022).

2.12.6 Personalised Asthma Action Plans (PAAPs)

Personalised Asthma Action Plans (PAAPs) are an integral part of asthma care, aimed at empowering individuals to take control of their asthma (NICE, 2017; BTS/SIGN, 2019; GINA, 2022). A PAAP, also known as a written action plan, a self-management action plan, or an individualised action plan, includes individualised self-management instructions (Bhogal, Zemek and Ducharme, 2006). These instructions are collaboratively devised with the patient and include baseline characteristics like lung function, maintenance medication, and guidance on how to respond to increasing symptoms and when to seek medical help (Gatheral *et al.*, 2017).

PAAPs are considered a key component of supported self-management for asthma patients (Pearce *et al.*, 2016).They are designed to enable people to both attain and regain control of asthma, especially in the event of an acute exacerbation (Bhogal, Zemek and Ducharme, 2006). The content of PAAPs typically includes objective cues for early detection of deteriorating asthma symptoms, prescribed medications, and actions to take during an acute episode. This may involve step-up and step-down therapy and instructions on accessing healthcare services. The format and design of action plans can

vary, but they inherently convey individualised self-management instructions (Gibson and Powell, 2004; Partridge, 2004; Gatheral *et al.*, 2017).

The role of PAAPs extends beyond simple management directives (Gibson and Powell, 2004). They promote self-management by reminding patients of their treatment plans, including which triggers to avoid, how and when to adjust treatment, and when to seek medical help. This approach aims to improve overall control of asthma symptoms (GINA, 2022). PAAPs also serve as an important communication tool between patients and healthcare professionals, functioning as a record and reminder of the discussions and agreements made between them (Welsh, Hasan and Li, 2011). The individualised nature of PAAPs allows for the tailoring of the plan to a person's experience of asthma, ensuring that it is relevant and effective for each individual patient and reviewed at least once every year (BTS/SIGN, 2019).

2.13 Back-to-School: A Significant Risk Factor for Asthma Exacerbations 'September Peak' in School-Aged Children

The return to school presents a significant risk factor for asthma exacerbations among school-aged children, contributing to a widely recognised global phenomenon known as the "September peak" (Sears and Johnston, 2007). There is indeed an increase in ED visits and admissions in September every year for asthma. This increase begins within 30 days after children return to school in September but is not observed after school returns in

January or March as shown in Figure 2.3 and 2.4 (Satia *et al.*, 2020). The "September peak" in childhood asthma exacerbations, noted in countries like Canada (Crighton, Mamdani and Upshur, 2001), the United States (Van Dole *et al.*, 2009), England and Scotland (Julious *et al.*, 2011). Scotland experiences a slightly earlier peak in hospital admissions for asthma compared to England, in line with the earlier commencement of the Scottish autumn term (Julious, Osman and Jiwa, 2007; Julious *et al.*, 2011). In Australia, the peak is observed in February, post the January summer holidays (Lincoln *et al.*, 2006). This pattern is not only a result of increased social interactions after summer holidays but a complex interplay of several factors (Bundle *et al.*, 2019).

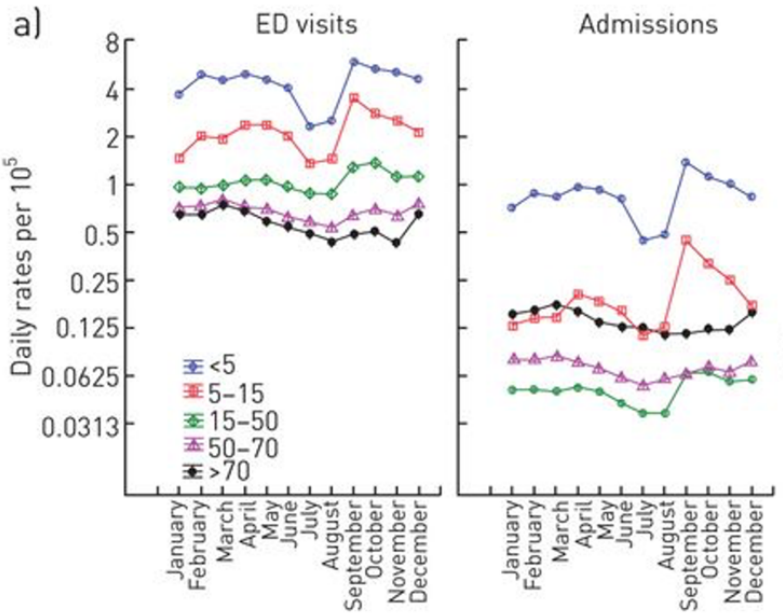


Figure 2-3 Mean daily rates of emergency department (ED) visits and admissions per 105 persons by month of the year from 2003 to 2013 for a) asthma (Satia *et al.*, 2020). Reproduced with permission of the © ERS 2024: ERJ Open Research 6 (4) 00593-2020; DOI: 10.1183/23120541.00593-2020 Published 2 November 2020

It is argued that one of the primary contributing factors to this peak is the surge in respiratory viruses, particularly rhinovirus (RV) and respiratory syncytial virus (RSV) (Johnston *et al.*, 2005). These viruses are potent asthma triggers, and the close-knit environment of schools facilitates their rapid spread among children (Johnston *et al.*, 2005; Sears and Johnston, 2007). Additionally, the start of the school year often exposes children to a range of indoor allergens, such as dust mites and molds, which are different from those at home. These allergens can significantly exacerbate asthma symptoms in sensitive individuals (Murray *et al.*, 2006).

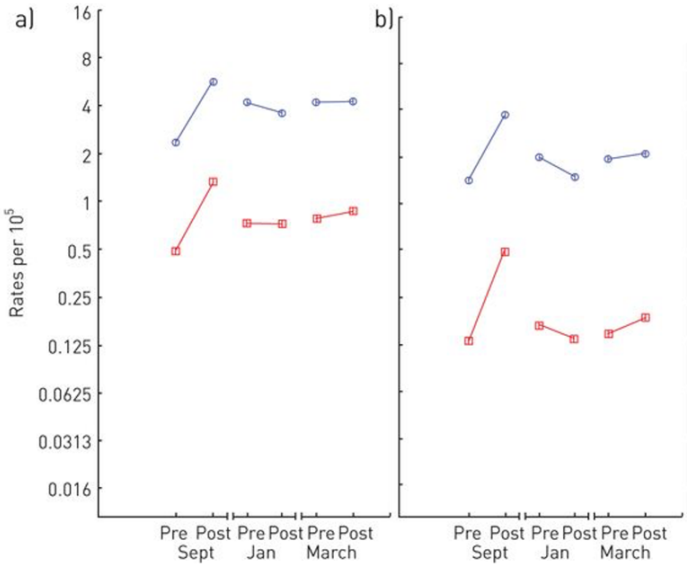


Figure 2-4 Asthma emergency department (ED) visit and admission rates per 105 persons averaged over the 30 days prior to (pre) and after (post) return to school after the summer (Sept), winter (Jan), and spring (March) vacation periods. a) Age <5 years; b) age 5–15 years. The y-axis is expressed on a log2 scale (Satia *et al.*, 2020). Reproduced with permission of the © ERS 2024: ERJ Open Research 6 (4) 00593-2020; DOI: 10.1183/23120541.00593-2020 Published 2 November 2020

The onset of a new school year can also be a source of stress and anxiety for many children, factors that are known to negatively impact asthma control (Wright, 2005; Rees,

2010; Tovey and Rawlinson, 2011; Landeo-Gutierrez *et al.*, 2020). Moreover, the summer break often leads to a decrease in consistent asthma medication uptakes, resulting in diminished asthma control by the time children return to school. This change in routine and the perceived reduction in symptoms during the holiday period contribute to this lapse in medication use (Sears and Johnston, 2007; Julious *et al.*, 2011; Tovey and Rawlinson, 2011).

Furthermore, schools may have varying levels of indoor air quality compared to homes, influenced by factors like ventilation and cleaning practices. Poor air quality in school environments can aggravate asthma symptoms (Daisey, Angell and Apte, 2003; Annesi-Maesano *et al.*, 2013). The peak in asthma exacerbations is most severe in school-aged children, but it also impacts families, leading to staggered peaks in asthma exacerbations across different age groups as viruses are transmitted to other family members (Johnston, 2006; Murray *et al.*, 2006).

Therefore, the term "September peak" doesn't simply mean a recovery from an "August trough." Instead, it represents a combination of various factors that coincide with the start of the school year, beginning in September and extending through autumn to December. Understanding this peak is crucial for healthcare systems due to its significant annual impact. Identifying children at higher risk for severe asthma symptoms during this period can lead to targeted educational and medical interventions, enhancing health

outcomes and reducing healthcare burdens. Initiatives like the PLEASANT trial were specifically designed to address and manage this seasonal challenge in asthma management effectively (Julious, Osman and Jiwa, 2007; Julious *et al.*, 2011).

The PLEASANT trial

2.13.1 Prior to PLEASANT

Asthma episodes and deaths have been shown to exhibit seasonal patterns, with several studies indicating peaks in asthma episodes among school-age children upon returning to school following summer vacation (Gergen, Mitchell and Lynn, 2002; Silverman, Stevenson and Hastings, 2003; Grech, Balzan and Distefano, 2004; Kimes *et al.*, 2004; Julious, Osman and Jiwa, 2007). When children return to school in the fall, they often come into close contact with allergens and catch respiratory infections from their classmates (Cai *et al.*, 2011; Krop *et al.*, 2014).

During summer holidays, routines can change and the risks of catching a cold or getting a respiratory infection might seem lower. This can lead to intentional reduction of preventive asthma medication use or unintentionally forgetting to take it (Johnston *et al.*, 2005; Sears, 2008). Furthermore, it is been reported that people who are only using bronchodilator therapy, without inhaled steroids or other preventive medications, tend to have higher rates of exacerbation (Johnston *et al.*, 2005; Murray *et al.*, 2006)

A prior study confirmed that unscheduled medical contacts with children with asthma increased around the time of returning to school, with children being approximately twice as likely as controls to have an unscheduled medical contact (Julious *et al.*, 2011). The same study revealed a 25% drop in inhaled corticosteroid prescriptions in August compared to July and September.

The factors associated with the decrease in prescriptions in August remain poorly understood. Research on adherence to paediatric asthma treatment has identified weak beliefs about the necessity of asthma medication as a key reason for non-adherence (Drotar and Bonner, 2009). The decline in asthma symptoms during summer months may contribute to weaker beliefs about the necessity of taking asthma medication (Julious *et al.*, 2018).

2.13.2 PLEASANT trial

The PLEASANT (Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term) trial aimed to address the decrease in prescriptions in August, which could be attributed to a lack of conviction regarding the importance of asthma medication due to the decline in symptoms during the summer months (Julious *et al.*, 2016). The study was an open-label cluster randomised trial, assigning GP practices to either the intervention or usual care. The trial evaluated whether a simple letter from a GP to parents of school-age children with asthma,

emphasising the importance of continuing to take asthma medication during the summer holidays, would reduce unscheduled contacts after the return back to school and increase prescriptions in August (Horspool *et al.*, 2013).

The PLEASANT trial recruited 142 GP practices, but one practice withdrew, resulting in 70 control and 71 intervention practices. The study included 12,179 children aged 5-16 and the data was collected for two years. The primary endpoint was the number of children with asthma who had at least one unscheduled medical contact at the start of the new school year in September. Additionally, the study examined 12 secondary endpoints, such as the number of patients with unscheduled medical contacts from September to December. Participants were divided into an intervention group, which received a reminder letter from their GP and a control group, which received standard care without a letter (Julious *et al.*, 2018).

The intervention was a simple letter sent out by the GP at the start of the school summer holidays (end of July 2013) which emphasised the importance of maintaining asthma medication adherence throughout the summer holidays. The letter was written in plain English and was designed by the study team, including a GP, health psychologist and consultant respiratory paediatrician. Also, it was discussed at patient and public events involving children with asthma and their parents. It addressed the importance of taking asthma medication and the risks associated with not doing so upon returning to school.

It also encouraged parent to contact the GP if they need more medication, have questions about the appropriate dosage, or require additional information (Horspool *et al.*, 2013).

The PLEASANT trial found no statistically significant effect on the primary outcome of unscheduled contacts in September. In fact, the data indicated a slight, non-statistically significant increase in unscheduled contacts among children in the intervention group. This lack of impact in September might be related to the timing of the assessment. September might have been too early to see the full effects of the intervention. It takes some time for viral infections to affect asthma symptoms in school-age children. So, the decision to focus on the first 4 weeks after school started might not have allowed enough time to see the intervention's true impact.

However, the intervention resulted in a 4% increase in the proportion of children collecting asthma prescriptions in August, from 12.6% to 16.5%. This represents an increase from approximately 13 to 17 children out of every 100 collecting their asthma prescriptions due to the intervention, demonstrating the intervention's effectiveness in improving medication uptakes during a period typically marked by a decline. However, it also highlights that the majority of children did not collect a prescription in August, indicating ongoing challenges in asthma medication uptakes during summer holidays. Furthermore, it's important to mention that the PLEASANT study did not look at prescriptions in September, a month in which an increase in prescription collection was

also observed in the intervention arm compared to the control group, as illustrated in Figure 2.3. This highlights the need for further investigation into the impact of the intervention in TRAINS including both August and September.

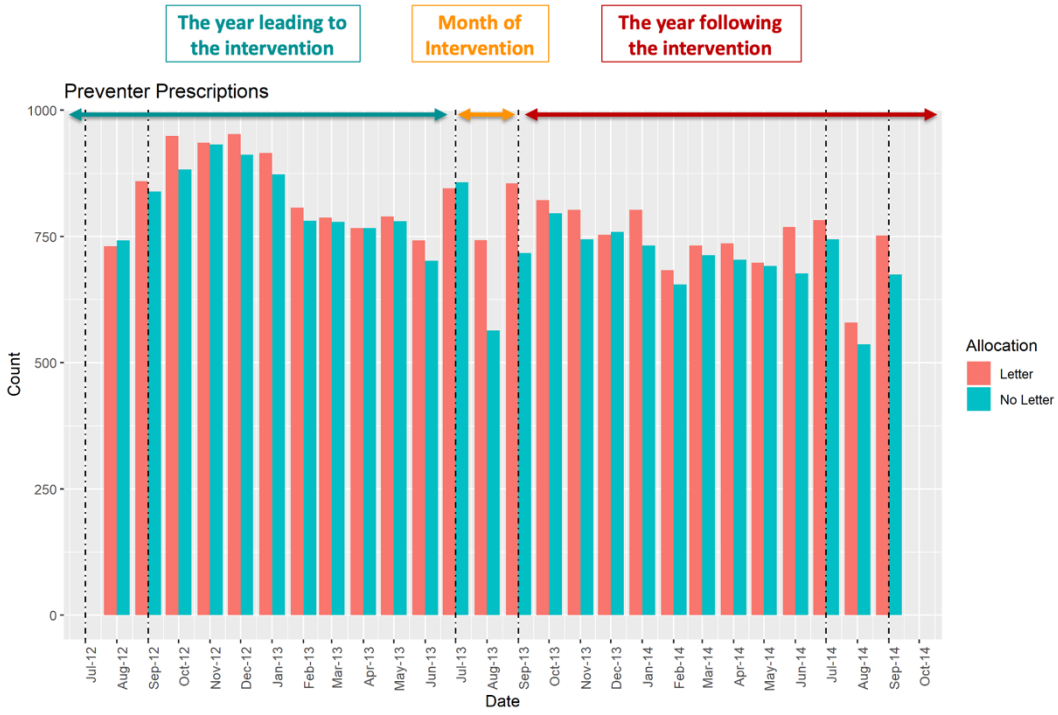


Figure 2-5 Monthly preventer prescription uptakes by children with asthma over time.

Despite not significantly impacting unscheduled contacts in September, the primary study outcome, the intervention led to a 5% reduction in total medical contacts over the 12-month period from September to August. This suggests a longer-term beneficial impact on healthcare utilisation, possibly attributable to improved asthma control facilitated by increased medication uptakes. The health economic analysis showed a mean cost-saving of £36.07 per patient over a year, reflecting the intervention's cost-effectiveness given the low cost of implementation (£1.34 per child) with a 96.3% probability. This aspect of the study underlines the potential for simple, cost-effective

interventions to make significant contributions to public health and healthcare expenditure. (Julious *et al.*, 2018).

To evaluate the clinical importance of this outcome, several factors need consideration. First, in chronic conditions like asthma, where consistent medication adherence is crucial for managing the disease and preventing exacerbations, any improvement in medication uptake can have significant implications. For patients with asthma, especially children, enhanced adherence could mean fewer exacerbations, less school absenteeism, and a reduced need for emergency healthcare services. Thus, from a clinical perspective, even a modest increase in the number of children adhering to their medication is valuable.

2.13.3 Summary of PLEASANT

The PLEASANT intervention was effective in modestly increasing the number of children obtaining asthma prescriptions during a typically low-adherence period. While it did not significantly reduce unscheduled care in September, the primary outcome, it did contribute to a reduction in total medical contacts in the year following the intervention. These findings highlight the potential of simple, cost-effective strategies in managing chronic conditions like asthma and suggest areas for further research and intervention development to enhance medication adherence. (Julious *et al.*, 2018).

It's important to note that improving medication adherence is a critical aspect of asthma management, and the PLEASANT study's results underscore this point. Children who

adhere to their preventers medication can have better control of their asthma symptoms and reduce the need for any medical contacts in the long term. Therefore, the intervention's success in increasing prescription collection is a positive step toward improving the asthma management of children with asthma. Moreover, the intervention's simplicity and low cost amplify its value. If a simple reminder can lead to an increase in medication uptake during a critical period, the intervention could be considered both efficient and scalable, with the potential for a broad impact when applied across larger populations.

In light of the PLEASANT study's outcomes, the TRAINS study aims to assess prescription uptakes in both August and September. . This expanded focus is informed by the observation from the PLEASANT trial where the data suggested that a prompt led to parents gathering prescriptions when it was necessary to do so – i.e. in August if prescription was due then or in September if due at that time. This behaviour can result in an increase in prescription pickups in both September and August. This observed pattern indicates a thoughtful approach by parents in managing asthma, where they align the collection of prescriptions with expected requirements, especially as their children return to school, where exposure to asthma triggers may become more frequent.

2.14 Conclusion

Throughout this chapter, we have addressed the issue of children with asthma in the UK. As the most common chronic disease in children, asthma has one of the highest prevalence in the UK compared to the rest of Europe. It has significant burdens both at an individual and societal level, extending far beyond health implications to include considerable economic costs for the healthcare system.

Furthermore, we navigated the "September peak" phenomenon, marked by a seasonal surge in asthma exacerbations among school-aged children in September. Various factors contribute to this pattern, including viral infections, suboptimal asthma treatment and changes in tolerance, emphasising the need to improve medication adherence during the summer holidays and as children return to school.

The PLEASANT trial has demonstrated that a simple postal intervention could markedly improve asthma outcomes for children with asthma in primary care. The study underscored the potential role GP practices could play, serving as direct, influential channels to remind parents about the importance of maintaining their children's asthma medication routines, particularly during the summer holidays. The success of the PLEASANT trial in increasing the prescription uptake during the summer holiday among children with asthma motivated and influenced this PhD project.

Our next focus is on implementing evidence-based approaches, specifically the PLEASANT intervention, in GPs. In the upcoming chapter, we will conduct a systematic review to explore the strategies and barriers associated with the implementation of such interventions. This will provide a valuable foundation for the TRAINS study intervention design to disseminate the PLEASANT trial findings among GPs, with the aim to ultimately promote better health outcomes for children with asthma in England.

Chapter 3: Printed Educational Materials as a Tool for Change: A Systematic Review of Letter-based Interventions Influencing Prescription Patterns in Primary Care Settings

3.1 Introduction

In this chapter, we assess the existing literature on the use of Printed Educational Materials (PEMs) as intervention methods to change prescription patterns in primary care settings and determine if any prior research has implemented an approach similar to the TRAINS project.

3.2 Chapter aims

The objectives of this chapter are to:

- To present the findings from a systematic review of studies on PEMs.
- To Explore how PEMs are carried out and their impact as interventions, particularly in modifying prescription patterns in primary care settings.
- To examine the structure and content of PEMs to gain a better understanding of their designing to help in design TRAINS intervention.

3.3 Background

In the previous chapter, we have addressed the issue of children with asthma, summer holiday and September peak and provided a summary of the PLEASANT trial intervention results to address this. To design the TRAINS project's intervention, which involves disseminating the PLEASANT trial's findings, we conducted a systematic review on the implementation of research findings about prescribing into practice using PEM.

A crucial aspect of healthcare is the timely translation of research findings into practice. However, a significant gap persists between research findings and their implementation, despite the considerable resources devoted to health sciences research (Straus, Tetroe and Graham, 2013). As a result, the potential benefits of evidence-based research often fail to reach many patients due to the lack of real-world application of recommendations (Grol, 2001; Schuster, McGlynn and Brook, 2005).

Knowledge Translation (KT) refers to a range of methodologies with the aims of getting research findings into practice (Straus, Tetroe and Graham, 2009). There are many terms used to describe this type of research, including: translational science, knowledge transfer; knowledge exchange; knowledge mobilisation; implementation science; research utilisation; and knowledge utilisation (Eccles and Mittman, 2006). The Cochrane Collaboration's Effective Practice and Organisation of Care (EPOC) group identified

various KT strategies, such as educational meetings, distribution of printed educational materials, educational outreach visits, audits and feedback, local opinion leaders, reminders and mass media. When well-designed, these KT interventions can significantly influence the behaviour of general practice practitioners (Grol and Grimshaw, 2003).

This systematic review focuses on methods and effects of PEMs interventions. PEMs, being straightforward and potentially cost-effective tools, facilitate the implementation of evidence-based research into practice (Giguère et al., 2020). They do this by disseminating published recommendations, clinical guidelines, articles in peer-reviewed journals, bulletins and monographs via mass mailing or personally (Grol and Grimshaw, 2003). A Cochrane review found that PEMs may have a significant effect on health professional practice outcomes (Giguère et al., 2020). Although randomised controlled trials (RCTs) have explored the use of PEMs interventions, gaps remain in our understanding of the optimal settings, the specific behaviours that can be influenced and ways to maximise the interventions' impact on various healthcare professionals (Grudniewicz *et al.*, 2015). Despite these gaps, PEMs, as affordable and low-tech interventions, continue to be used independently or in combination with other interventions to disseminate clinical guidelines, new evidence and crucial information (Grudniewicz *et al.*, 2015)

This systematic review aims to assess the design and implementation of PEMs in previous studies that aim to influence prescription patterns among primary care clinicians. The findings will be used to inform the design of the intervention for the TRAINS study. The target population for this review includes general practice practitioners and physicians within primary care settings.

Objectives:

- Population: general practice practitioners and physicians within primary care settings.
- Intervention: PEM interventions delivering research-based information to influence prescription patterns.
- Comparison: Usual care (non-interventions) or other single or multi-component educational interventions.
- Outcome: Changes in prescription patterns, with a primary focus on asthma prescriptions

This systematic review initially had a specific focus on asthma preventer medications. However, due to the limited number of relevant studies, it was expanded to explore the use of PEMs for changing prescription patterns in a broader context.

3.4 Method:

3.4.1 Literature search

We adapted and refined a search strategy from a prior review for this systematic review, which aimed to understand how PEMs influence knowledge, behaviour and patient outcomes among primary care providers compared to no intervention or other types of educational interventions (Grudniewicz et al., 2015). Our focus was specifically on PEMs related to drug prescription.

We conducted systematic searches on the MEDLINE(R) and EMBASE databases, using search terms that included freely used text and applicable MeSH headings such as message, print, book, pamphlet, educational materials, monograph, email, book, journal, primary care physicians, family physicians and general practitioner. The search was narrowed to studies published in English between January 2000 and 27th September 2020 (refer to Appendix A for the detailed Medline search strategy). The start date of January 2000 was chosen to ensure the review focused on relatively contemporary studies, reflecting modern medical practice, technologies, and methodologies. This timeframe would provide relevant insights for the current healthcare landscape and the design of the TRAINS project intervention. The search was later updated in May 2023 (from January 2000 to May 2023). Additionally, we examined the reference lists of the included studies and relevant reviews for further resources.

3.4.2 Inclusion criteria:

Studies were included based on the following characteristics:

1. Studies should be designed as randomised controlled trials (RCTs) or cluster randomised trials (CRTs).
2. The subjects should be primary care physicians and healthcare providers, such as family physicians, specialists in primary care settings and paediatricians.
3. PEM interventions should aim primarily at implementing research, like guidelines, feedback, recommendations and the dissemination of published or unpublished information and evidence-based content in printed or electronic form. Electronic forms could be document files, PDFs and non-interactive web pages.
4. The goal of the intervention should be to influence prescription patterns.
5. All methods of delivering PEMs interventions, such as mail, email and fax, are acceptable.
6. The measured outcomes should involve changes in prescription uptake. Initially, we focused on asthma prescriptions but later expanded to general prescriptions.

3.4.3 Exclusion criteria:

The following types of studies were excluded:

1. Studies using interactive online educational materials, such as online workshops or courses, as these are not part of the TRAINS project.
2. Studies not in English or published outside the period from 2000 to 27th September 2020.
3. Studies with outcomes related to attitudes.

3.4.4 Data extraction

We conducted a comprehensive data extraction process from each study included in our review. The process involved two independent reviewers to enhance the accuracy and reliability of the extracted data. Any differences in screening and extraction between the reviewers were resolved through thorough discussion and consensus. The extracted data focused on several key details as follows:

Study Details: We documented the title, year of publication and the country where each study was conducted. This helped provide context and potential cultural or regional influences on the studies.

Study Design: We noted the research design of each study, such as whether it was a RCT or a cRCT. Understanding the methodology used provided us insights into the robustness of the results.

Target Prescription: We recorded the specific types of prescriptions the interventions in each study targeted. This allowed us to understand the scope of the problems the interventions sought to address.

Intervention Type: We classified the type of intervention carried out in each study. This included interventions such as postal bulletins, outreach visits, emailing educational newsletters, or a combination of these methods.

Printed Materials: We identified the specific types of printed educational materials used in each intervention. This included materials such as evidence-based guidelines or recommendations.

Number of PM Versions: We noted the number of different versions of printed materials used in the interventions, which gave us an understanding of the depth and variety of the content provided to the participants.

Frequency of Mailing: We recorded the frequency at which the educational materials were mailed or delivered to the participants in each study. This allowed us to assess the intensity of the interventions.

Number of Participants: We documented the number of participants in each study. This helped us evaluate the scale of each study and potentially the strength of its findings.

Comparator: We recorded the type of comparator used in each study. This ranged from controls (non-intervention groups) to comparisons with other types of educational interventions.

The data extraction form used in Appendix B further outlines the specific variables and details extracted from each study. For more detailed information on the data extracted from each study, refer to Table 3.1.

3.4.5 Quality assessment of the studies

The quality assessment of the included studies was performed using the Cochrane EPOC Risk of Bias Assessment Tool. Most studies demonstrated low risk in crucial areas like random sequence generation and allocation concealment. Nevertheless, high or unclear risk was observed in a few studies concerning baseline characteristic measurement and protection against contamination. Incomplete outcome data and selective outcome reporting were areas of high risk in certain instances. Generally, the knowledge of allocated interventions appeared to be of low risk, indicative of sufficient blinding across the studies. While interpreting the results, these factors ought to be taken into account. For a detailed breakdown, please refer to Table 3.2.

3.5 Result

3.5.1 Search results

The initial literature search identified 866 articles. After removing 182 duplicate entries, we screened the remaining 684 articles by title and abstract. This led to the exclusion of 628 articles, leaving us with 56 full-text articles for further evaluation. From these, 12 studies fulfilled the inclusion criteria and were selected for review. The process of selection is illustrated in Fig 3.1.

3.5.2 Characteristics of the included studies

The 12 selected studies were either randomised controlled trials (RCTs) or cluster randomised trials (CRTs), conducted between 2002 and 2021. Half of the studies (six) originated from Canada (Pimlott *et al.*, 2003; Beaulieu *et al.*, 2004; Dormuth *et al.*, 2004, 2012; Zwarenstein *et al.*, 2016; Howie *et al.*, 2021), while two were carried out in Ireland (Naughton, Feely and Bennett, 2007, 2009) and Denmark each (Søndergaard *et al.*, 2002, 2003) and one each in the UK (Guthrie *et al.*, 2016) and Italy (Perria *et al.*, 2007). These studies targeted a broad range of drug prescription. Across the 12 included studies, participant numbers ranged from 98 to 4504. Detailed characteristics of each study can be found in Table 3.1.

The quality of the studies was evaluated using a risk of bias assessment. The assessment considered several key factors, such as random sequence generation, allocation concealment, baseline outcome measurement, baseline characteristic measurement, handling of incomplete outcome data, knowledge of allocated interventions, protection against contamination, selective outcome reporting and other potential sources of bias.

Most studies exhibited a low risk of bias across multiple categories. For instance, six studies demonstrated low bias risk in the majority of categories. However, some studies, accounting for two in this case, had high or unclear risks in some areas, particularly in dealing with incomplete outcome data and selective outcome reporting. Moreover, the majority of the studies had low or unclear risk in protection against contamination.

Notably, several studies showed an unclear or high risk in the 'other' category, which may encompass a variety of potential bias sources not covered by the main categories. These findings emphasise the importance of thorough and cautious interpretation of results, considering potential biases that may affect the study outcomes.

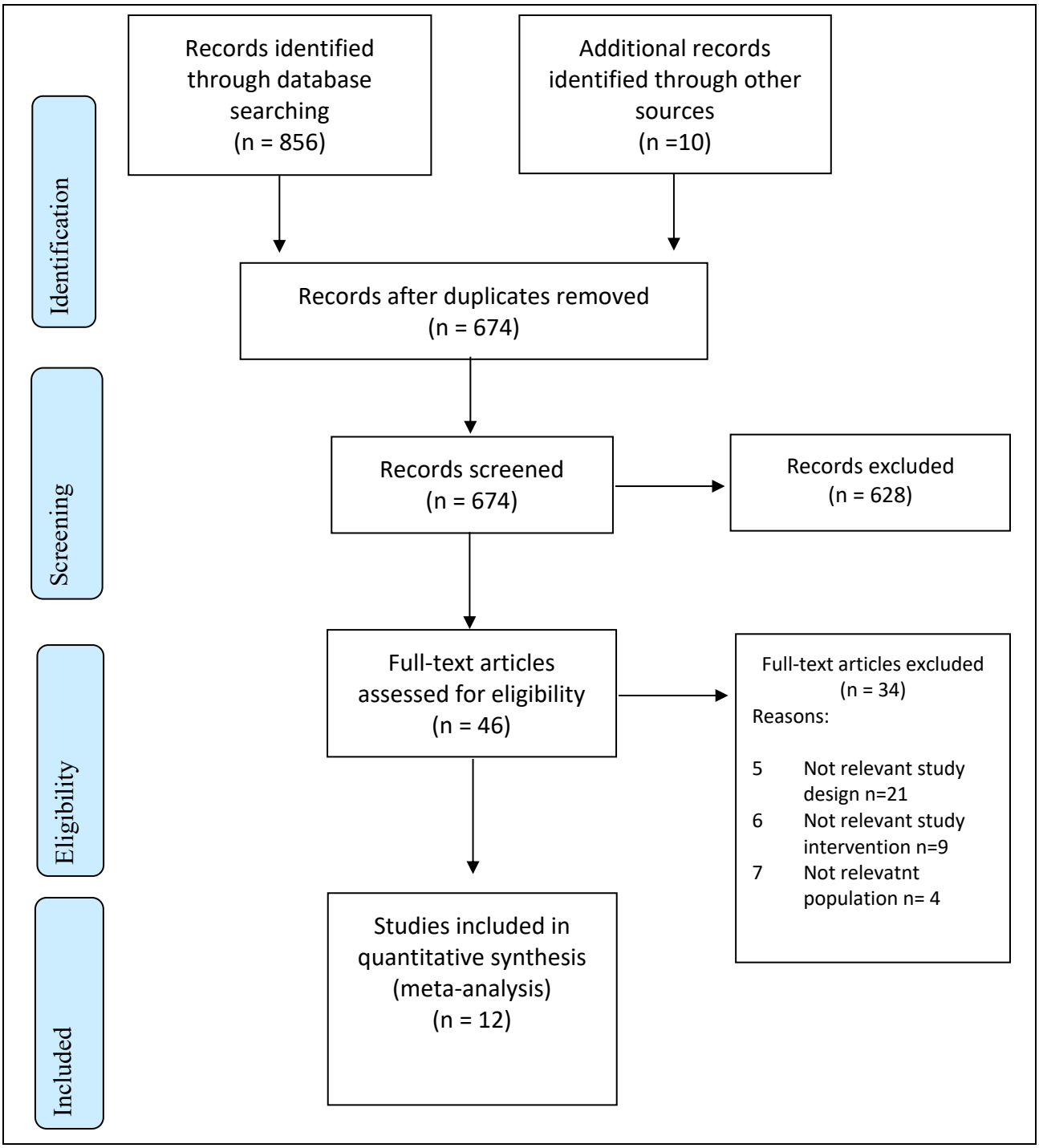


Figure 3-1 PRISMA flow chart of selection process for the included studies in the review

Study and year	setting	Study design	Target prescription	Intervention	Printed materials	# of PM version	Frequency of mailing	# of participants	Comparator
Søndergaard J (2002)	Denmark	RCT	Asthma (Preventer)	Postal bulletin	Recommendation and guideline	3	3	292 GPs (178 practices)	Multi-intervention
Pimlott N (2003)	Canada	RCT	Sedative (benzodiazepine)	Postal bulletin	Recommendation and evidence-based	2	3	168 physicians	Another intervention
Søndergaard J (2003)	Denmark	RCT	Respiratory infection (antibiotics)	Postal booklet	Feedback and guideline	1	1	299 GPs (181 practices)	Another intervention
Beaulieu M (2004)	Canada	RCT	Stable angina pectoris	Postal a one-page summary of guidelines or the summary plus reminder	Guidelines	1	1, 2	2326 physicians	Control, Multi-intervention
Dormuth C (2004)	Canada	CRT	12 medications*	Postal bulletin	Evidence-based	12	1	499 physicians	Delayed intervention
Perria C (2007)	Italy	RCT	Type 2 diabetes	Dissemination of guidelines (postal) or (training course and dissemination of guidelines)	Guidelines	1	1	252 GPs	Control, Multi-intervention
Naughton C (2007)	Ireland	CRT	CVD preventive, Diabetes	Postal bulletin or (postal bulletin plus outreach visit)	Recommendation	1	1	110 GPs (99 practices)	Another intervention
Naughton C (2009)	Ireland	RCT	Respiratory infection and Otitis (Antibiotics)	Postal bulletin or (postal bulletin plus outreach visit)	Recommendation	1	1	98 practices	Another intervention
Dormuth C (2012)	Canada	RCT	Statin	Postal bulletin	Recommendation	1	1	2725 physicians	Delayed intervention
Guthrie B (2016)	UK	CRT	prescribing safety	Emailing educational newsletter	Recommendation, feedback	6	5	262 practices	Multi-intervention
Zwarenstein M (2016)	Canada	CRT	Hypertension (thiazides)	Postal two types of PEMs	Evidence-based practice synopsis	4	1	4504 physicians	Multi-intervention
Howie A (2021)	Canada	CRT	Diabetes management	Postal two types of PEMs	Guideline recommendations	2	1	4231 practices	Control, Multi-intervention

Table 3-1 Characteristics of included studies.

*The 12 medications for Dormuth study are Cimetidine, Metronidazole/(amoxicillin or tetracycline), ASA/Ibuprofen/naproxen, Isosorbide dinitrate, Thiazide diuretics, Combined effect, Hormones, Calcium-channel blockers, Clonazepam/alprazolam/ diazepam, Finasteride, Long-acting benzodiazepines, and Calcium-channel blockers. Control (no intervention)

Study	Random sequence generation	Allocation concealment	Baseline outcome measurement	Baseline characteristic measurement	Incomplete outcome data	Knowledge of allocated interventions	Protection against contamination	Selective outcome reporting	Other
Søndergaard J (2002)	Low	Low	Unclear	Low	Low	Low	Low	Low	High
Pimlott N (2003)	Low	Low	Low	High	Unclear	Low	High	Low	Low
Søndergaard J (2003)	Unclear	Low	Low	High	Low	Low	High	Low	Low
Beaulieu M (2004)	Low	Low	Unclear	Unclear	High	Low	Low	Unclear	High
Dormuth C (2004)	Low	Low	Unclear	Low	Low	Low	Low	Low	Low
Perria C (2007)	Low	Low	Low	Low	High	Low	Low	High	Low
Naughton C (2007)	Low	Unclear	Low	Low	Low	Low	High	High	High
Naughton C (2009)	Low	Low	Low	Low	Low	Low	High	Unclear	High
Dormuth C (2012)	Unclear	Unclear	Low	Low	Low	Low	High	Unclear	Low
Guthrie B (2016)	Low	Low	Low	Low	Low	Low	High	Unclear	Low
Zwarenstein M (2016)	Low	Low	Unclear	Low	Low	Low	High	Low	Low
Howie A (2021)	Low	Low	Unclear	Low	Low	Low	Low	Low	Low

Table 3-2 Risk of Bias of Included RCT studies Using Cochrane EPOC Risk of Bias Assessment Tool

3.5.3 Interventions

Each study used various types of PEMs as interventions. These included feedback, guidelines and evidence-based content. Feedback materials were utilised in three studies (Naughton, Feely and Bennett, 2007, 2009; Guthrie *et al.*, 2016). Guidelines were prominent in five studies (Søndergaard *et al.*, 2002, 2003; Beaulieu *et al.*, 2004; Perria *et al.*, 2007; Howie *et al.*, 2021). Lastly, evidence-based materials were featured in four studies (Pimlott *et al.*, 2003; Dormuth *et al.*, 2004, 2012; Zwarenstein *et al.*, 2016). The delivery of these interventions was primarily through postal mail, with email used in one study (Guthrie *et al.*, 2016). Of the 12 studies, only three studies provided their intervention materials (Dormuth *et al.*, 2012; Guthrie *et al.*, 2016; Zwarenstein *et al.*, 2016).

3.5.4 Comparison

The group comparison designs across the twelve included RCTs were significantly diverse, each implementing unique strategies and targeted interventions. These ranged from traditional postal feedback and information bulletins to more comprehensive approaches such as academic detailing.

The twelve included RCTs varied widely in their group comparison designs, each deploying unique interventions ranging from traditional postal feedback and information bulletins to more comprehensive approaches like academic detailing.

Four studies (Søndergaard J 2003, Pimlott N 2003, Naughton C 2007, Naughton C 2009) implemented a design in which two intervention groups were compared directly (one intervention vs another intervention), aiming to evaluate the efficacy of distinct intervention strategies applied within identical participant demographics.

Two studies (Dormuth C 2004 and Dormuth C 2012) presented a unique design, comparing an immediate intervention group to a delayed intervention group, enabling the observation of any changes over a longer period of time.

Finally, Six studies (Søndergaard J 2002, Beaulieu M 2004, Perria C 2007 Guthrie B 2016, Zwarenstein M 2016, Howie A 2021) employed a multi-arm design, introducing several distinct intervention strategies to be compared against a single intervention group. This design can give insights into the relative effectiveness of various interventions applied concurrently. Among these six and the total of twelve studies, only three (Beaulieu M 2004 and Perria C 2007, Howie A 2021) included a control group that received no intervention. This allows us to measure the impact of the intervention when compared to those who didn't receive any intervention. These comparisons are further detailed in Table 3.3

RCTs	Message	Intervention Design and Groups			Delivery	Statistical significance effect
		1st Group	2nd Group	3rd Group		
Søndergaard J (2002)	↑ ↑ Motivate GPs to improve their prescribing of corticosteroids	To receive a one-page with a large-font letter as feedback that includes a simple table of patient count data in the middle of the page.	To receive aggregate data on asthma drug prescribing patterns and a guideline.	To receive feedback on irrelevant topic and considered as control group.	Postal	No effect
Pimlott N (2003)	↓ ↓ To reduce the prescribing of long-acting benzodiazepines	The 1st group is assigned to receive bulletins of evidence-based educational coupled with confidential profiles of benzodiazepine prescription use were mailed every 2 months for 6 months.	To receive educational bulletins and feedback about first-line antihypertension drug prescribing for elderly patients.		Postal	No effect
Søndergaard J (2003)	→ To evaluate the impact of postal feedback dissemination on prescribing antibiotics plus a clinical guideline on treating respiratory tract infections versus the clinical guideline alone.	To receive clinical practice guidelines on the treatment of respiratory tract infections and postal feedback with aggregated data on their prescribing patterns for antibiotics.	To receive the guidelines only and served as control group.		Postal	No effect
Beaulieu M (2004)	→ To study the effects of guideline dissemination on physicians' prescribing practices for the treatment of stable angina pectoris.	To a summary of clinical guidelines on the treatment of as a one-page (in February 1999).	To receive the summary plus a reminder (in February and March 1999, respectively).	To receive no intervention (controls).	Postal	No effect
Dormuth C (2004)	↑ ↓ To measure the impact of a series of evidence-based drug therapy letters mailed to physicians in British Columbia on prescribing to newly treated patients.	To receive a Therapeutics Letter (a concise bulletin of 2 to 4 colourful pages) includes 12 issues of an evidence-based series.	To receive the letters 3–8 months after the intervention group and served as control group.		Postal	No effect
Perria C (2007)	→ To assess the management of noncomplicated type 2 DM among GPs of the Lazio region.	To receive a two-day training course with CME credits and dissemination of the guideline.	To receive the clinical guideline with a written request to implement it without any training.	To receive no intervention (controls).	Postal	No effect

Naughton C (2007)	↑ ↑ To increase the level of (1) statin prescribing in patients with CVD; (2) antiplatelet prescribing in patients with coronary artery disease and (3) antiplatelet and statin prescribing in diabetic patients.	To receive postal bulletin plus outreach visit. The bulletin was composed of educational information and individualised GP prescribing feedback displayed using graphs and included the actual number of GP-registered patients who did not receive recommended treatment.	To receive the postal bulletin only.		Postal	No effect
Naughton C (2009)	↓ ↓ To reduce the overall rate of antibiotic prescribing.	To receive bulletin feedback about antibiotic prescribing for respiratory tract infection and otitis media based on UK guidelines.	To receive the postal bulletin plus academic detailing (outreach visit).		Postal	Positive effect
Dormuth C (2012)	↓ ↓ To reduce new statin prescribing for primary prevention.	To receive an early intervention which was a personalised prescribing portrait on statins that included therapeutic recommendations.	To receive a delayed personalised portrait.		Postal	Positive effect
Guthrie B (2016)	↓ ↓ To reducing high risk prescribing	To receive usual care consisting of emailed educational material with support for searching to identify patients.	To receive usual care and feedback on practice's high risk prescribing, quarterly on five occasions.	To receive the usual care and the same feedback incorporating a behavioural change component.	Email	Positive effect
Zwarenstein M (2016)	↑ ↑ To increase the choice of thiazides as the first-line treatment for people newly diagnosed with hypertension.2	Practices were randomly assigned to receive one of six intervention groups: 1. informed only (no PEM) 2. informed plus insert 3. informed plus outsert a. Atheoretical outsert b. TPB-based outsert 4. informed plus insert and outsert a. Atheoretical outsert b. TPB-based outsert "Informed was a free, evidence-based practice synopsis, peer-reviewed, mailed primary care providers. Two types of PEMs addressed the identified evidence-practice gap: a two-page article, indistinguishable from the rest of the newsletter in size and style (the "insert") and two versions of a short, directive, evidence-based PEM on a postcard-sized card stapled to the front page of informed (the "outsert")".			Postal	No effect
Howie A (2021)	To improve adherence to guideline recommendations for diabetes care through treatment intensification.	Practices were randomly assigned to receive one of four intervention groups: 1. a postcard-sized message ("outsert") 2. a longer narrative article ("insert"). 3. Both insert and outsert 4. Neither (Usual care)			Postal	No effect

Table 3-3 The intervention design of each study

3.5.5 Study duration

Outcomes were measured one year post-intervention at the cluster level in five studies (Søndergaard *et al.*, 2002, 2003; Perria *et al.*, 2007; Zwarenstein *et al.*, 2016; Howie *et al.*, 2021). Three studies evaluated the impact of the interventions over a period of 24 months, with 12 months prior to intervention and 12 months post-intervention (Pimlott *et al.*, 2003; Naughton, Feely and Bennett, 2009; Dormuth *et al.*, 2012). Two studies conducted follow-ups after 6 months of the intervention (Beaulieu *et al.*, 2004; Naughton, Feely and Bennett, 2007). One study evaluated effects three months post-intervention (Dormuth *et al.*, 2004), while another assessed impact 15 months after intervention implementation (Guthrie *et al.*, 2016).

3.5.6 Prescription pattern outcome

Among the included studies, three studies (Naughton, Feely and Bennett, 2009; Dormuth *et al.*, 2012; Guthrie *et al.*, 2016) demonstrated a significant change in prescription patterns. On the other hand, the remaining studies (Søndergaard *et al.*, 2002, 2003; Pimlott *et al.*, 2003; Beaulieu *et al.*, 2004; Perria *et al.*, 2007; Zwarenstein *et al.*, 2016; Howie *et al.*, 2021) did not show statistically significant results. However, slight changes in prescription patterns were observed in two studies (Søndergaard *et al.*, 2002; Pimlott *et al.*, 2003). Interestingly, one study that employed 12 issue of evidence-based intervention letters reported a statistically significant outcome when the cumulative effects of combining all

the letters (Dormuth *et al.*, 2004). The statistical outcomes of the PEMs on prescription patterns for each study are represented in Table 3.4.

Author and Year	Study Title	Reported Measure (if available)	Result
Søndergaard J (2002)	Detailed postal feedback about prescribing to **asthma** patients combined with a guideline statement showed no impact: a randomised controlled trial	Incidence rate (95% CI)	Incidence of initiation of inhaled steroids among 1650 **repeat users** of inhaled b2-agonists. Feedback with patient-count data: 0.013 (0.011, 0.017), Feedback with aggregated data: 0.014 (0.011, 0.018), Control group: 0.018 (0.015, 0.021) Incidence of initiation of inhaled steroids among 3704 **first-time users** of inhaled b2-agonists. Feedback with patient-count data: 0.064 (0.054, 0.076), Feedback with aggregated data: 0.054 (0.045, 0.066), Control group: 0.060 (0.052, 0.069)
Pimlott N (2003)	Educating physicians to reduce benzodiazepine use by elderly patients: a randomized controlled trial	P-value	p = 0.036 (significant difference for one measure, but not others)
Søndergaard J (2003)	Mailed prescriber feedback in addition to a clinical guideline has no impact: a randomised, controlled trial	Mean Diff. (95% CI)	Diff. in change (Intervention minus control) Mean (95% CI) −0.6 (−2.8;1.6)
Dormuth C (2004)	Effect of periodic letters on evidence-based drug therapy on prescribing behaviour: a randomized trial. (The intervention was 12 issues of an evidence-based series called Therapeutics Letter)	Relative risk (95% CI)	No letter achieved statistical significance on its own (Inhaled corticosteroids RR 2.36 (95% CI 0.67 – 9.20)). However, when the 12 letters effect was combined, the overall result was significant RR 1.30 (95% CI 1.13–1.52)
Beaulieu M (2004)	Drug treatment of stable angina pectoris and mass dissemination of therapeutic guidelines: a randomized controlled trial	Odds Ratio (95% CI)	b-Blockers 1.00 (0.88,1.13), Antiplatelet 1.05 (0.94,1.18), and Hypolipaemics 1.02 (0.90,1.16)
Perria C (2007)	Implementing a guideline for the treatment of type 2 diabetics: results of a Cluster- Randomized Controlled Trial (C-RCT)	Odds Ratio (95% CI)	OR 1,06 [0,76–1,46], OR 1,07 [0,80– 1,43], OR 1,4 [0,91–2,16]
Naughton C (2007)	A clustered randomized trial of the effects of feedback using academic detailing compared to postal bulletin on prescribing of preventative cardiovascular therapy	β-Coefficients and 95% CI	3% increase in statin prescribing in CVD patients at 6 months post-intervention for both randomized groups, but no statistical difference (β = 0.004; 95% CI = –0.01 to 0.02)

Naughton C (2009)	A RCT evaluating the effectiveness and cost-effectiveness of academic detailing versus postal prescribing feedback in changing GP antibiotic prescribing	β-Coefficients and 95% CI	Immediately post intervention PB (β = -0.02, 95% CI -0.04, -0.001) and AD (β = -0.02, 95% CI -0.03, -0.001) practices significantly decreased overall antibiotic prescribing. No significant differences between the randomized groups in the immediate or long-term post-intervention period. €88 vs €778 cost comparison for services.
Dormuth C (2012)	A Randomized Trial Assessing the Impact of a Personal Printed Feedback Portrait on Statin Prescribing in Primary Care	Relative risk (95% CI)	Compared to the delayed control group, the relative probability of a new statin prescription for primary prevention decreased by 6% in the 12 months after. adjusted RR 0.94 (95% CI 0.91–0.98)
Zwarenstein M (2016)	Printed educational messages fail to increase use of thiazides as first-line medication for hypertension in primary care: a cluster randomized controlled trial	Odds Ratio (95% CI)	OR for insert effect was 0.98 (95% CI 0.87 to 1.11), OR for outsert effect was 0.93 (95% CI 0.83 to 1.05), both insert and outsert was 1.00 (95% CI 0.89 to 1.12)
Guthrie B (2016)	Data feedback and behavioural change intervention to improve primary care prescribing safety (EFIPPS): multicentre, three arm, cluster randomised controlled trial	Odds Ratio (95% CI)	In the primary analysis, high risk prescribing as measured by the primary outcome fell from 6.0% (3332/55 896) to 5.1% (2845/55 872) in the usual care arm, compared with 5.9% (3341/56 194) to 4.6% (2587/56 478) in the feedback only arm (odds ratio 0.88 (95% confidence interval 0.80 to 0.96) compared with usual care; P=0.007) and 6.2% (3634/58 569) to 4.6% (2686/58 582) in the feedback plus behavioural change component arm (0.86 (0.78 to 0.95); P=0.002).
Howie A (2021)	Printed educational materials directed at Ontario family physicians do not improve adherence to guideline recommendations for diabetes management: a pragmatic, factorial, cluster randomized controlled trial	Odds Ratio (95% CI)	OR for outsert 1.01 (95% CI 0.98 to 1.04), OR for insert 0.99 (95% CI 0.96 to 1.02)

Table 3-4The results of the PEMs on prescription patterns for each study.

3.5.7 Theoretical use of behaviour change

Among the 12 reviewed papers, a majority of 10 studies did not provide information on the utilisation of behavioural theories in their interventions. In contrast, the remaining two studies applied the theory of planned behaviour (TPB) (Guthrie *et al.*, 2016;

Zwarenstein *et al.*, 2016). However, the presence of a theoretical basis did not reveal a statistically significant correlation with intervention effectiveness across the intervention arms, as outlined in Table 3

3.5.8 Multiple interventions outcomes

In terms of multiple intervention outcomes, two RCTs reported that academic detailing was not significantly more effective than a postal bulletin in altering prescription patterns. (Naughton, Feely and Bennett, 2007, 2009). Similarly, one study found no significant difference between the impacts of a comprehensive two-day training course (with continuing medical education credits and guideline dissemination) and only receiving the clinical guideline (Perria *et al.*, 2007).

3.6 Discussion

In this systematic review, we explored the use of PEMs in influencing the prescription patterns of GPs. While PEMs offer a cost-effective way to address gaps in GP practices, our review shows that their effectiveness is variable, with only one study assessing the effect of email. This highlights the importance of optimising their utilisation and exploring ways to improve their impact.

Originally, we aimed at understanding the influence of PEMs on the prescription of asthma preventer medications. However, due to a lack of relevant studies, we expanded

the review to involve other prescription patterns, revealing a significant research gap and underscores the need for additional targeted studies.

The heterogeneity in reported measures (e.g., odds ratios, relative risks, incidence rates) and outcomes across these studies reflects the methodological diversity in this field. This diversity, while offering a broad view, also poses challenges in synthesising and drawing definitive conclusions.

The statistical outcomes of the studies on the impact of printed educational materials (PEMs) on prescription patterns reveals a nuanced picture. While some studies, such as Pimlott N's 2003 research, demonstrate a statistically significant effect in specific contexts (e.g., reducing benzodiazepine use among the elderly), others, like Søndergaard J's studies in 2002 and 2003, show little to no statistical impact on prescribing behaviours. This variability underscores the complex nature of influencing prescriber behaviour through educational materials. In cases where statistical significance is noted, it's crucial to differentiate between statistical and clinical significance, as the real-world impact on patient care may vary. Additionally, the studies highlight the importance of context, suggesting that the effectiveness of PEMs is likely dependent on various factors such as the specific medical condition, the target audience, and the method of implementation. This heterogeneity in outcomes indicates that while PEMs can be a valuable tool in certain

scenarios, their overall effectiveness in changing prescription patterns is not uniformly guaranteed and requires a more tailored approach.

Given this heterogeneity, conducting a meta-analysis was not suitable for this systematic review. The wide range of study designs, populations, interventions, and outcomes found in the literature makes it difficult to combine data in a meaningful way that would provide a clear, unified conclusion. Meta-analyses require a level of homogeneity in the studies being reviewed to accurately combine and compare results. The significant differences in contexts, conditions targeted, and implementation methods in studies involving PEMs introduce too much variability, making it challenging to draw overarching conclusions through a meta-analysis. This decision underscores the necessity of considering each study's unique context and outcomes when evaluating the effectiveness of PEMs in influencing prescribing behaviours.

The successful interventions from the studies that showed statistically significant improvements in GPs' prescription patterns suggest that well-designed PEMs can potentially influence practices. Specifically, studies by Dormuth et al. (2012) and Guthrie et al. (2016) highlight the effectiveness of well-designed printed educational materials (PEMs). These studies underscore the importance of incorporating visual aids such as charts and ensuring a reader-friendly layout to enhance the efficacy of PEMs. The use of visual aids can simplify complex information, making it more accessible and actionable

for GPs. Additionally, Guthrie et al.'s success in using email for delivery points to the potential benefits of digital distribution. (Dormuth *et al.*, 2012; Guthrie *et al.*, 2016). Guthrie et al. (2016) also used email in its delivery. These findings provide a promising a direction for future research to understand how the design and presentation of PEMs can influence their effectiveness. On the contrary, studies like Søndergaard J (2002) and Howie A (2021) did not report significant impacts, which could be due to a variety of factors including the relevance of content, the methodology of delivery, or the absence of supplementary supportive measures.

Our review also made an interesting observation regarding the effectiveness of single and multi-component interventions. While it may seem logical to assume that combining multiple approaches would lead to better results, our findings showed that simple postal bulletins were just as effective as more complex multi-component interventions (Naughton, Feely and Bennett, 2007, 2009; Perria *et al.*, 2007). This finding highlights the importance of quality over quantity in intervention design and could inform the development of more cost-effective strategies in future.

Furthermore, our review sheds light on the theoretical foundations of behaviour change interventions. Notably, only two of the 12 studies reviewed explicitly employed a behaviour change theory, specifically the Theory of Planned Behaviour (TPB). Both Zwarenstein et al. (2016) and Guthrie et al. (2016) utilised TPB in their designs, yet their

findings offer limited clarity on the definitive impact of this theoretical approach. Zwarenstein et al. did not observe a significant difference in effectiveness between TPB-based and atheoretical interventions, while Guthrie et al. found similar effect sizes for interventions with and without TPB components. These results suggest that the direct contribution of TPB or any specific behaviour change theory to the effectiveness of interventions in healthcare settings is complex and not straightforward.

The varied group comparison designs, ranging from direct two-group comparisons to multi-arm comparisons, underscore the heterogeneity inherent in the included studies. An active control was also the most common comparison with only one study - Dormuth *et al.*, 2004 – being a two arm trial comparing to an arm which could be considered usual care. The effects of these interventions varied across the studies, some showing no effect while others demonstrating statistical significance, illustrating the wide range of impacts these interventions can have in different contexts. This diversity in outcomes highlights the need for customised, context-specific interventions in order to achieve optimal effects.

The review has some limitations. The diversity of study designs, interventions and outcome measures across the analysed studies made it challenging to draw definite conclusions. Also, a significant limitation was the unavailability of intervention materials in many studies. This absence made it challenging to make comprehensive comparative analyses and understand why certain interventions succeeded while others did not.

Future trials could benefit from enhanced transparency, allowing for a more comprehensive understanding of each intervention.

3.7 Conclusion

In conclusion, the impact of PEMs on GPs' prescription patterns remains an open question. The existing literature offers mixed results, some indicating promising outcomes while others showing minimal impact, though the one study which used email did show a positive effect. As it stands, this review does not provide conclusive evidence that PEMs lead to significant changes in prescription patterns, clinician behaviours, or patient outcomes.

It remains challenging to determine whether the tested PEMs have been fully optimised and if the intervention has achieved adequate reach. Published studies lack sufficient details regarding the development of these materials (including the utilisation of theory, evidence-based design, and end-user involvement) and provide only limited descriptions of the materials used.

This review was initiated in September 2020 and was later updated in May 2023. This update led to the identification of an additional study, which supplemented our understanding of PEMs' impact but did not significantly alter our overall conclusions.

This systematic review, including twelve trials published between January 2000 and May 2023, provides insight into the various factors that affect the effectiveness of PEMs. The heterogeneity of study designs and outcomes emphasises the need for well-structured, large-scale trials and calls for a greater focus on simplicity and design in the creation of PEMs. Our review also identifies a significant gap in research concerning PEMs' influence in paediatric asthma treatment, which we intend to address in this project.

Our findings suggest that well-designed PEMs, particularly those with simple, clear messaging, could potentially influence GPs' prescription patterns when compares to usual care. This supports the possibility that PEMs could be a cost-effective way to address healthcare gaps. However, to strengthen these initial findings, future research needs to address the limitations identified in the existing evidence, such as inadequate information, inconsistent outcome measures and the lack of available intervention materials.

Therefore, we decided to use PEMs for the TRAINS study which is supported by several strategic considerations that align with the unique advantages of PEMs in disseminating research findings and influencing healthcare practices. These considerations include:

1. **Cost-effectiveness and Resource Efficiency**: Given the constraints of our budgets and the need for scalable interventions, PEMs offer a cost-effective solution for disseminating information widely without incurring significant expenses. Their

affordability and ease of distribution make them particularly suitable for large-scale studies like TRAINS, aiming to reach a broad audience of healthcare providers.

2. **Accessibility and Flexibility**: PEMs can be easily accessed and used by healthcare professionals at their convenience, allowing them to engage with the material at their own pace and according to their own schedules. This accessibility is crucial for ensuring that the information reaches and impacts the intended audience. Furthermore, PEMs' flexibility in format and content means they can be quickly updated or modified to reflect the latest evidence or guidelines, ensuring that the information remains relevant and timely.

3. **Potential to Fill a Specific Research Gap**: The TRAINS study identified a specific gap in the literature regarding the use of PEMs to influence the prescription of asthma preventer medications in school-aged children. By focusing on this area, the study aims to provide targeted insights into how PEMs can be effectively utilised to improve prescribing practices for a critical patient population, thereby addressing a significant need within GPs.

4. **Opportunity for Digital Integration**: With the increasing digitalization of healthcare information, the TRAINS study also recognises the opportunity to explore digital or hybrid formats of PEMs, such as using email for dissemination.

This approach reflects a modern understanding of PEMs' role in a digital age, potentially enhancing their reach and impact.

Moving forward, the potential for PEMs to positively influence GPs prescribing and contribute to improved patient outcomes compared to usual care in a two arm design warrants further exploration – particularly if using both mail and email. The PLEASANT intervention has shown promise in improving the prescription of asthma preventers in children and we aim to use PEMs to disseminate these results. By addressing the findings of this review about the interventions, we hope to design an effective intervention for TRAINS project. The next chapter will outline the design for the TRAINS project in more detail.

Chapter 4: The Development and Design of The Intervention Materials

4.1 Introduction:

The previous chapter presented the systematic review of using PEM to influence GP practices. This chapter provides detail of the comprehensive process that went into developing and designing the intervention materials for the TRAINS study. The focus of this chapter is the evolution of the intervention design through various stages, each bringing unique insights to refine the intervention. From systematic reviews to, GPs seminars, steering committee meetings and consultations with a communication expert.

4.2 Aims of the chapter:

- To outline the methodology employed in the development and design of the intervention materials.
- To discuss the insights gained from the systematic review, GPs seminars, TSC meetings and a communication consultant contact.
- To present the final results of the design of the intervention.

4.3 Overview

Knowledge Translation (KT) plays a critical role in the healthcare, bridging the gap between research findings and their application in clinical practice(Straus, Tetroe and Graham, 2009). This process is vital for transforming research into practical strategies that significantly uplift healthcare quality and effectiveness (Grimshaw *et al.*, 2012). The gap between evidence-based recommendations and actual clinical practice highlights a critical KT deficiency, showcasing the gap between "what is known" (and/or recommended) and "what is practiced" (Davis *et al.*, 2003). The difference between evidence-based recommendations and actual clinical practices underscores the importance of better integrating research findings into everyday healthcare. This integration can lead to improved patient outcomes and more efficient healthcare delivery (Eccles and Mittman, 2006).

Over time, the definition of translational gaps has changed, leading to a universally accepted 5-phase framework (T0-T4) for identifying these gaps (table 4.1) (Fort *et al.*, 2017). Table 4.1 highlights the systematic nature of translating research into practical healthcare outcomes. Translating research finding like PLEASANT into practice, a focus of the TRAINS study, represents a T3 gap in knowledge translation. This gap specifically focuses on translating research findings into significant improvements in patient

outcomes and healthcare practices. The following table highlights the systematic nature of translating research into practical healthcare outcomes:

Gap	Definition	Explanation
T0	Translation to Discovery	Engages in foundational scientific research to uncover new insights and address unmet health needs.
T1	Translation to Humans	Transfers discoveries from basic research into clinical applications, initiating trials in human subjects.
T2	Translation to Best Practice Recommendations	Validates the clinical effectiveness of interventions, leading to the development of clinical guidelines.
T3	Translation to Widespread Use	Focuses on the adoption and integration of evidence-based practices and guidelines into healthcare settings.
T4	Translation to Impact at Population Level	Assesses the broader impact of implemented interventions on population health outcomes and effectiveness.

Table 4-1 Translational Gap Definitions.

EPOC group has identified several KT strategies. These include educational meetings, distribution of PEMs, educational outreach visits, audits and feedback, utilisation of local opinion leaders, reminders, and mass media campaigns. Each of these strategies aim to facilitate the dissemination and implementation of research evidence into clinical practice, ultimately improving healthcare delivery and patient outcomes (Grimshaw *et al.*, 2012).

As clarified in the previous chapter, PEMs were chosen as a key intervention for the TRAINS study due to their crucial role in bridging the gap between research findings and their application in clinical practice settings (Grudniewicz *et al.*, 2016). Their familiarity,

accessibility and economical nature make them a cost-effective intervention within healthcare settings (Giguère *et al.*, 2020). (PEMs) can enhance patient care by advocating for evidence-based clinical practices and discouraging ineffective procedures (Gagliardi, Alhabib, and and the members of the Guidelines International Network Implementation Working Group, 2015).(Gagliardi, Alhabib, and members of the Guidelines International Network Implementation Working Group, 2015)

When designing PEMs, studies indicate that GPs often prefer evidence summaries to primary studies due to their ease of use, highlighting the importance of designing PEMs that are accessible and actionable (McColl *et al.*, 1998; Guyatt *et al.*, 2000; Kunz *et al.*, 2007). This preference highlights the necessity for PEMs to be not only informative but also pragmatically designed. Straus and Haynes (2009) emphasise the "3Rs" of evidence-based communication: reliability, relevance, and readability, which are vital for the effectiveness of PEMs (Straus and Haynes, 2009). However, the literature on KT often lacks practical guidance on how to achieve these criteria.

The Medical Research Council (MRC) offers guidance on developing, evaluating, and implementing complex interventions, advocating for a flexible and iterative approach. This guidance emphasises the importance of stakeholder engagement and theory-informed design, critical for tackling the complex nature of health behaviours and systems (Craig *et al.*, 2008). The success of PEMs lies not only in their content but also

significantly in their design and development. Aligning these materials with the preferences and practical realities of end-users, such as healthcare professionals, is crucial (Grudniewicz, Bhattacharyya, *et al.*, 2015). Furthermore, emphasising the importance of aligning interventions with specific contexts highlights the need for tailored approaches (Michie, van Stralen and West, 2011). This approach informed our iterative and participatory design process, involving direct feedback from GPs, communication consultant and other stakeholders. By stakeholders, we refer to those who directly interact with or are impacted by these materials, which includes healthcare professionals. This process reflects the principles highlighted by Grudniewicz et al. (2015), advocating for the involvement of end-users in the development of healthcare interventions to ensure their practicality and relevance (Grudniewicz, Bhattacharyya, *et al.*, 2015).

Also, the design of interventions should draw behaviour change theories. These theories offer insights into the factors that can influence the effectiveness of PEMs, particularly in the context of healthcare change implementation and quality improvement (Grol *et al.*, 2007; Stergiou-Kita, 2010; Greenhalgh *et al.*, 2017). For example, the Health Belief Model (HBM), the Theory of Planned Behaviour (TPB), the Social Cognitive Theory (SCT), and the Transtheoretical Model (TTM) stand out for their widespread application in designing health interventions. The HBM (Rosenstock, 1974) and TPB (Ajzen, 1991), with their focus on individual beliefs and intentions, respectively, offer insights into the cognitive processes behind health behaviours. The SCT adds a layer of complexity by

considering the effects of social environments and self-efficacy (Bandura, 1986), while the TTM provides a roadmap of the stages people go through as they change their behaviour (Prochaska and DiClemente, 1983).

The TRAINS study leverages the HBM theory that offers insights into the decision-making process of healthcare providers, suggesting that the perceived benefits and barriers significantly influence their engagement with new practices (Rosenstock, 1974). According to this model, informing GPs of the PLEASANT study's results aims to influence their perceptions of the severity of asthma exacerbations after returning to school (perceived severity) and their susceptibility to improve preventers uptake during the summer holiday (perceived susceptibility). The intervention suggests that if GPs believe the benefits of following the PLEASANT study's insights (perceived benefits) outweigh the barriers (perceived barriers), such as time or effort required to change prescription patterns, they are more likely to implement these recommendations.

Similarly, the TPN has been instrumental in understanding the motivational factors that impact GP behaviours (Ajzen, 1991). This theory is crucial for understanding GPs' intentions behind prescription changes. It examines how attitudes, influenced by the PLEASANT study outcomes, along with subjective norms and perceived control, shape GPs' prescribing behaviours. The goal of sharing the PLEASANT study results is to

positively influence these factors, steering GPs towards improved asthma prescription uptake during the summer holiday.

The application of HBM and TPB in the TRAINS intervention underscores their relevance in addressing the behaviours of healthcare providers like GPs, blending an understanding of individual and social behaviour determinants to promote the adoption of PLEASANT intervention results in clinical settings.

This chapter will present comprehensive details regarding the design of the intervention and our engagement with GPs to develop an intervention that is practical and feasible for implementation. We will discuss the steps taken to create the intervention that effectively addresses the identified needs and aligns with the context of healthcare delivery.

4.4 Methodology

The methodology adopted for the TRAINS study was structured to thoroughly understand the design and content preferences valued by GPs in in PEMs. This objective was pursued through a multifaceted approach, including two GP seminars, a systematic review detailed in Chapter 3, the establishment of the TRAINS Trial Steering Committee (TSC), and consultation with a communication specialist. These components were strategically chosen to ensure a comprehensive gathering of insights and to refine the intervention's language and presentation, aiming to enhance the uptake and usability of PEMs. The development and design of the intervention spanned a six-month period, from November 2020 to April 2021, allowing for an iterative refinement process based on ongoing feedback and emerging insights (Figure 4.1).

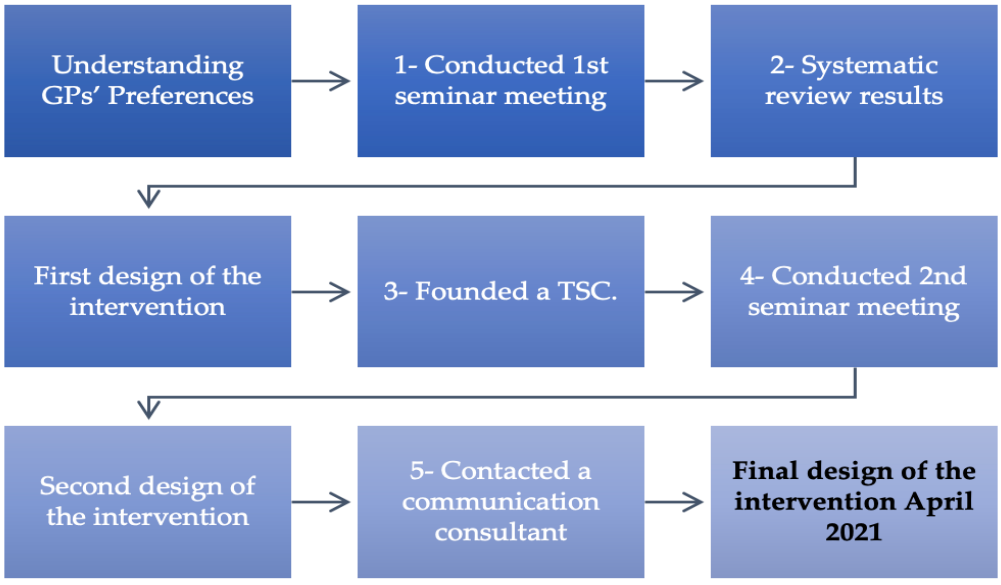


Figure 4-1 Flowchart of the development of the intervention.

During the GP seminars and TSC meetings, we engaged in-depth with GPs to identify the design and content attributes deemed crucial for increasing the uptake of PEMs. These discussions highlighted a strong preference for materials that are not only scientifically sound but also closely aligned with the practical needs and daily realities of GPs. This emphasis on relevance and applicability reflects the core findings of Grudniewicz et al. (2015), underscoring the importance of creating PEMs that effectively bridge the gap between research evidence and clinical practice (Grudniewicz, Bhattacharyya, *et al.*, 2015).

Furthermore, the intervention's development was guided by key principles derived from behaviour change theories, notably the HBM and the TPB. These theories provided a foundational framework for understanding the cognitive and motivational factors influencing GPs' engagement with new practices. By incorporating these theoretical insights, the intervention was designed to address perceived benefits and barriers, enhancing GPs' willingness to adopt evidence-based recommendations within their practices.

The collaborative input from the TSC and the targeted advice from a communication specialist were instrumental in refining the intervention's messaging, ensuring clarity, persuasiveness, and effectiveness. This comprehensive methodology, characterised by its stakeholder-driven, theory-informed, and iterative nature, represents a robust approach

to developing an intervention that is both evidence-based and finely tuned to the needs of its intended audience.

4.5 Phases of development and design

4.5.1 First seminar January 2020

The first seminar was our starting point for making the intervention. The goal was to bring healthcare professionals into the process to better understand how to share evidence and what they need.

4.5.1.1 Method

We conducted a face-to-face seminar meeting with a group of 16 attendees at the Academic Unit of Primary Care, Northern General Hospital, Sheffield, England. The participants included salaried GPs, GP partners, locum GPs, as well as educators, researchers, GP trainees and medical students.

The seminar was divided into two parts. Initially, we presented details about the TRAINS project, which included the outcomes of the PLEASANT trial, the objectives of TRAINS, our study design, the intervention, participants, methodology and timeline. The second part was to gather feedback about the intervention and discussing several aspects, including the optimal method and timing of delivery and the type of information to include in the intervention (refer to Table 1).

4.5.1.2 Results

4.5.1.2.1 Delivery of the intervention (Letter vs Email)

During the discussion, all participants agreed that combining letters and emails for the intervention would be more effective than relying on a single mode of delivery. One suggestion was to integrate the letter into the "SystmOne" system, along with helpful tools and search templates to simplify GPs' tasks. It was advised to avoid using Docmail, as it was found that most people did not have access to it. Additionally, it was emphasised that reaching out to the asthma lead in practices is crucial, as they usually have clinical leads in various areas, including asthma (Table 4.1).

4.5.1.2.2 Intervention Content

The participants gave some suggestions on how to grab attention when presenting research findings about the benefits of reduced mortality in children with asthma and fewer appointments. They recommended using quotes, anecdotes and discussing the potential for reduced workload. It was also suggested to include a link to a website with additional information and tools. The participants believed that it is important to avoid overwhelming people with too much information and to carefully consider who the information is being presented to.

4.5.1.2.3 Timing of sending the intervention

Most of the participants recommended sending the intervention multiple times. Specifically, they suggested sending the first email in February to emphasise the importance of the PLEASANT results and the need to implement the study. The second email in April would encourage GPs to prepare for implementation, while the final email in June would serve as a reminder to send a letter before summer holiday begins.

Design Questions	Details	Select Participant Quotes
Question 1: What is the best way to share or send the intervention? To Whom?	• Letter vs Email	*"Depends on who it goes to."* *"It is better to send it to the practice manager or a named GP."* *"Maybe send it to asthma lead"*
Question 2: What should I mention in the intervention besides the PLEASANT study to get GPs' attention?	• Reduce hospital admission • Cost saving	*"Providing headlines such as reduced mortality in children and reduced appointments felt to be a good way of getting attention."* *"Giving quotes or anecdotes, mentioning possible decreased workload."*
Questions 3: Timing of the intervention/letter?	• Before the summer holiday	*"No point as a single shot"* *"If x3 email approach taken then consider Feb, April, June"* *"Sending more than one email like "softener" email, followed by a further 2 emails."*

Table 4-2 Participant Preferences for the Design of Printed Educational Materials; 1st Seminar

4.5.1.3 Discussion

The feedback we received from the seminar was extremely useful for our project. We gained valuable insights from the GPs on topics such as study design, intervention development and the best timing for intervention distribution. We agree with the recommendation to distribute the intervention through both mail and email. Additionally, we believe that highlighting the reduction in hospital admissions and cost-saving benefits would help to promote the implementation of our results. Finally, the suggestion to distribute the intervention multiple times before the summer vacation aligns with our goal of giving practices enough time to take action.

4.5.1.4 Conclusion

The first seminar was important in guiding our intervention's design. The key takeaways from the seminar, such as using both email and letters, delivering the intervention in stages and presenting information that is engaging and easy to understand, will shape how we develop the intervention. These insights will help us create a practical and effective intervention.

4.5.2 Systematic review September 2020

To gain a deeper understanding of the factors influencing GPs' actions and the essential design elements of intervention letters, we conducted a systematic review of contact

strategies with GPs using PEMs. For detailed information, please refer to Chapter 3. The aim of this review was to examine the specific features of PEMs interventions that could potentially modify GPs' prescription behaviours by analysing the available evidence.

Our systematic review provided several key insights for our intervention's design. We learned that clear, evidence-based content in PEMs could influence GP behaviours. We also identified the importance of including relevant feedback mechanisms and the potential impact of repeated intervention delivery.

Interestingly, one study showed a significant effect with email as the delivery method, suggesting the need to explore various delivery options in our intervention.

The review was limited as only three studies provided the actual PEMs used in their papers, but these served as a starting point for our understanding. With these insights, we aim to develop a simple and direct, evidence-based PEM intervention that effectively influences GP prescription behaviours. The intervention will be delivered multiple times and will also explore the use of email as a delivery method.

4.5.3 First version of the intervention November 2020

Informed by the Health Belief Model (Rosenstock, 1974) and the Theory of Planned Behaviour (Ajzen, 1991), we designed the first version of the intervention letter by integrating insights from the systematic review and the GP seminar. The Health Belief

Model guided our emphasis on the importance of continuing taking preventers medication during the summer holiday and the benefits of sending reminder letters during this period. Meanwhile, the Theory of Planned Behaviour influenced our approach to making actionable recommendations easily accessible to GPs. With these theoretical underpinnings, we developed two draft versions of the intervention letter:

- A detailed version (2 pages – four-sided)
- A brief version (1 page – two-sided)

Both versions addressed the observed decrease in preventers prescription uptake among children with asthma during the summer holidays and highlighted the crucial need of maintaining regular asthma preventive medication in August. They also brought forward the outcomes of the PLEASANT trial (Julious *et al.*, 2018), encouraging GP practices to remind parents about the importance of their children taking preventers asthma medication throughout the summer holidays.

The detailed version contained graphs and included the reminder letter used in the PLEASANT trial (Version 1). On the other hand, the brief version provided links for downloading a similar reminder letter (Version 2). Both of these versions can be found in the Appendix C.

4.5.4 TRAINS Trial Steering Committee (TSC) meeting February 2021

One of the steps that was taken to enhance the intervention and oversee the progress of the study, was to establish the TRAINS Trial Steering Committee (TSC). The TSC's role was to provide advice on the first version of intervention and to supervise the overall trial.

4.5.4.1 Method

We conducted a meeting with TSC members, where we sought feedback on the intervention design. We discussed aspects such as timing, frequency, recipients, length and delivery approach. The TSC consists of two Academic GPs, a Practice Nurse, a Practice Manager and a Statistician.

4.5.4.2 Results

4.5.4.2.1 Intervention Content: (Long vs short)

TSC Members suggested providing more information about cost-saving benefits. The shorter version of the letter was favoured by most participants, who suggested making it less verbose and more visual, using simple, direct language. Emphasising potential cost savings for practices was thought to be effective. There was also a consensus that patients tend to respond better to text messages than to letters (Table 4.2).

4.5.4.2.2 Timing of the intervention (May and June)

The majority of the members proposed sending the intervention in May and June. One participant suggested extending the delivery period to April, May and June, offering GPs a larger window to implement the study. It was also advised to send the intervention more than once. The idea of including a sample reminder letter with the intervention was also suggested.

4.5.4.2.3 Delivery of the intervention (Letter vs Email)

Opinions varied on whether the intervention should be delivered via mail or email. Some raised concerns about the effectiveness of email, citing the high volume of emails that practices often receive, which could potentially be overlooked or deleted. However, one participant observed that practices have diverse preferences, some favouring emails and others mail. Thus, distributing the intervention both via email and mail might suit all practices.

4.5.4.2.4 Targeting: (clinicians vs managers)

In discussing the intervention's intended audience, one participant suggested prioritising clinicians over managers due to the clinical nature of the content. Another idea was to target asthma nurses or leads, as they conduct asthma reviews and are ideally suited

recipients. However, it was noted that this could vary from practice to practice, as clinical leads may not always take action in every setting.

Design Questions	**Details**	**Select Participant Quotes**
Question 1: Intervention Content: Information? Long or short	• Long vs short • Cost saving	*"Be less wordy and more visual"* *"If there is a cost saving they goanna be interested"*
Question 2: Timing of the intervention?	• May and June	"*Definitely May and June and may be April, May and June. June is too late"* *"May and June to give practice more time."*
Questions 3: Delivery of the intervention):	• Letter vs Email	*"Emails to practice managers will probably get deleted"* *"Send both every practice is different so might cover what they want."* *"A letter with a sample letter"* *"Any validation of whether the practises received this is useful"*
Questions 4: Targeting (To whom?)	• Clinicians vs Managers	*"This is more clinical, you need to be targeting clinicians rather than practice mangers."* *"Nurses really might be a good reach"* *"Where I set now I would say send it to the clinical lead because they will do it and deal with it, in the practice that I was in before I would say send it to practice manager because it wouldn't get action by clinician lead"*

Table 4-3 TSC's Preferences for the Design of The Intervention

4.5.4.3 Discussion

The TSC meeting was very important in shaping our intervention. It gave us valuable insights on how to get GPs' attention and get them to take action. The advice about the timing of the intervention and the delivery methods were in line with the initial recommendations from the first seminar. Given this the feedback, we decided to send the short version of the letter twice, through both email and mail, to the asthma lead and practice manager in May and June.

4.5.4.4 Conclusion

The TSC meeting showed us that we need to have a flexible approach when it comes to our intervention. We learned the importance of using clear language, sending the intervention in different ways and carefully choosing who gets the intervention. We also saw the benefits of sending the intervention more than once. This advice guided us in creating an intervention that works well and fits the different needs and likes of different practices.

4.5.5 Second seminar March 2021

A follow-up seminar was conducted to present the findings of the systematic review and to get feedback on the proposed intervention.

4.5.5.1 Method

The seminar was conducted online by the Academic Unit of Primary Care, Northern General Hospital, Sheffield, England. It brought together the same group of GPs and other professionals who were present at the first seminar. The seminar aimed to seek feedback on the two proposed intervention versions, one short and one long. Participants were encouraged to express their preferences regarding these templates and provide insights on how to gain GP attention effectively. Furthermore, we invited discussion on the timing and method of delivering the intervention and the intended recipients.

4.5.5.2 Results

4.5.5.2.1 Which intervention do you prefer? (Long or short letter)

Most of the group preferred the shorter version of the intervention letter. They thought it should be clear, to the point and show the benefits of the implementation. They also thought it would be helpful to talk about how the intervention could reduce hospital visits and save money. It was suggested that including a leaflet about our PLEASANT trial could help get doctors' attention (table 4.3).

4.5.5.2.2 When to send the letter?

When the participants were asked when to send the letter, the majority commented that May and June. A minority of participants indicated that just May or June. However, all agreed to send the intervention early, giving GPs more time to act on the letter if they wish to.

4.5.5.2.3 How to send the letter?

Opinions were divided on the most effective delivery method: some suggested email for its convenience and traceability, while others felt that post might get more attention. A combined approach, using both email and postal methods, was also proposed.

4.5.5.2.4 To whom?

The primary targets for the intervention, as suggested by the majority, were the asthma clinical lead and the practice manager. One participant also recommended including the practice pharmacist.

Design Questions	Details	Select Participant Quotes
Question 1: Intervention Content: Information? Long or short	• Long vs short • Get attention	*"I prefer the short version"* *"Reducing unscheduled care in Autumn"* *"Less it's good to emphasise that this could save both practice attendances with exacerbations and hospital admissions"*
Question 2: When to send intervention?	• May and June	*"May and June"* *"May"*
Questions 3: How to send the intervention):	• Letter vs Email	*"both"* *"Email* *"A letter with a sample letter"* *"Any validation of whether the practises received this is useful"*
Questions 4: To whom?)	• Asthma clinical lead • Practice manager	*"Asthma clinical lead."* *"Practice pharmacist +asthma lead (probably a nurse)"* *"Asthma clinical lead and practice manager"* *"Both"*

Table 4-4 Participants' Preferences for the Design of the Intervention; 2nd seminar

4.5.5.3 Discussion

The feedback gathered in this seminar aligned closely with the suggestions received from the TSC meeting. The agreement was that the short letter was preferred, the method of delivery should be mixed (both email and postal), the intervention should be sent in May and June and the target audience should be the asthma clinical lead and the practice manager. The emphasis on reducing unscheduled hospital admissions was repeated throughout the seminars and TSC meeting, highlighting its importance in potentially easing GP workload.

4.5.5.4 Conclusion

The second seminar underscored the preference for the shorter intervention template and supported previous findings regarding intervention timing and delivery. It also highlighted key targets for the intervention - the asthma clinical lead and the practice manager. Based on these valuable insights, we decided to finalise the shorter intervention letter, enhance its content and accompany it with a leaflet, reminder letter and SMS template for GPs to use.

4.5.6 Revised intervention letter (short version) and plan March 2021

Taking into account the feedback from the TSC and the second seminar, we decided to use the short letter (the brief version) for the intervention. We planned to send this letter both via email and mail, once in May and again in June, targeting the Asthma Clinical Lead and Practice Manager. To encourage successful implementation, we decided to supplement the letter with a reminder letter and SMS text template. We also chose to attach a leaflet that outlines the PLEASANT trial offering the reader a more thorough understanding of the preventers medication declines in children with asthma during the summer holiday and the increased of the unscheduled visit to GPs after returning to school and the learnings from PLEASEANT study intervention. Furthermore, we decided to include a link to the PLEASANT trial's website, ensuring access to in-depth details on the trial, its publications and relevant resources. The revised version of the intervention can be found in Appendix D.

4.5.7 Finalising the intervention: Communication consultant collaboration April 2021

As the final step in our intervention development process, which had already included a systematic review, two seminar meetings with GPs and inputs from the TSC, we enlisted the expertise of communication consultant, Lucy Harper. With her extensive experience writing for both NHS England and Leicester City's Public and Patient magazine, Harper

was a valuable resource for enhancing the communicative effectiveness of our intervention (Harper, 2021).

4.5.7.1 Method

This final step of refining our intervention involved a series of meetings and discussions with Harper. The objective was to transition our scientifically toned draft into language that would be both accessible and appealing to the GPs. We presented Harper with our intervention materials and she provided insights into making them more understandable and engaging. Through the meetings, we aimed to keep the essence of the original work intact while making it more accessible. Harper suggested several changes to the drafts, which we reviewed thoroughly. Some changes, such as rephrasing "children with asthma" to " asthmatic children," were not in line with our patient-centred narrative, so we maintained the original terminology. However, most of Harper's recommendations were integrated into the intervention.

Additionally, the collaboration aimed to ensure the intervention materials were not only informative but also visually appealing and easy to read. The areas of improvement were broadly categorized into:

a) Copywriting, designing and printing the intervention letter and leaflet.
b) Creating a clear, scannable and easy-to-read email.
c) Developing simple, brief and persuasive reminder letters.

4.5.7.2 Results

After several rounds of revisions and discussions, Harper presented us with the modified intervention materials. She had liaised with a designer to refine the visual layout and style of the letters and leaflet. With a few minor adjustments, we approved her work. The final versions of the GP letter, leaflet, reminder templates (letter and SMS text for GPs' use) and email were then prepared.

4.5.7.3 Discussion

Our collaboration with Harper was essential in our intervention design process. The consultation effectively transitioned our initial drafts into a more comprehensible, appealing package for GPs. Not only was the language made accessible, but the visual layout and style of the materials were also enhanced, potentially improving the reception of our intervention among GPs.

4.5.7.4 Conclusion

This critical step aimed to ensure that the intervention was not only disseminated effectively but was also likely to be well received by its intended audience. We hoped this attention to detail, including the transformation of our scientifically toned drafts into a language more appealing to GPs, would prove beneficial in the real-world application of

the intervention. The final version of the intervention reflects our commitment to a comprehensive and considerate process we undertook in its development.

4.6 Results

4.6.1 Final version of the intervention April 2021

The final version of the intervention, completed in April 2021, is the result of five stages of consultations: discussions with GPs, insights from a systematic review, guidance from the TSC and the expertise of a communication consultant.

This intervention package includes a tailored letter to GPs, which, containing recommendations and helpful links, specifically underscores the decline in preventer medication collection during summer holidays and highlight its importance for children with asthma, along with presenting the results of the PLEASANT study. The package also contains a detailed leaflet about the PLEASANT study. Additionally, reminder templates are provided to assist GPs in implementing the intervention.

Moreover, an email with all the intervention materials attached had been prepared for ease of dissemination. These materials are available in Appendix E. For more specific details about the intervention design are available in Table 4.4.

Element Design	Details
Length	• Letter to GPs is two pages • Leaflet is two pages • A template reminder letter is one page • Template reminder SMS is 245 characters • Short paragraphs and bullet points. • Easy to read
Layout	• When appropriate, two columns are preferred versus one column. • Two-sided pages to make it easier to post the materials • By using bold and detailed headings that explain the contents of the following section, GPs can quickly locate useful information and decide if the letter interests them.
Design	• The intervention design is simple to attract GPs • Use of white space • Use soft colour schemes that are not too bright or light and pale. • Use clear division headings between sections.
Topic Visibility and Accessibility	• The topic and title are bolded and clear to help direct the reader's attention.
Messages & Key Points	• Main messages outlined, coloured and highlighted • Make the intervention purpose clearer
Recommendation	• Brief and clear • The purpose was made clear
Timing	• May and June

Table 4-5 Design details for the intervention Materials.

4.7 Discussion

The development of our intervention was a complex and iterative process, heavily influenced by the insights and feedback from a diverse range of stakeholders. Central to this process was the integration of feedback from GPs, findings from a systematic review, recommendations from the TSC, and the expertise of a communication consultant. The resulting intervention is thus a product of multi-faceted input, designed to be both accessible to and effective for GPs.

Significant modifications made during the development process were directly informed by behaviour change theories, particularly the Health Belief Model and the Theory of Planned Behaviour. These theories guided our focus in the intervention materials on the broader benefits of following best practices in asthma management. One key aspect highlighted in the GP's letter and leaflets was the importance of adherence to preventers medication during the summer holiday. Additionally, the intervention incorporated findings from the PLEASANT trial, which demonstrated the positive impact of sending reminder letters to parents, such as increased prescription uptake, reduced unscheduled care, and cost savings for the health service. This strategy aligns with the HBM by emphasising the practical benefits and effectiveness of these practices. By combining these theoretical insights and concrete evidence, the intervention aims to strengthen GPs'

confidence in the recommended actions and encourage their implementation, ensuring the materials are both effective and applicable in clinical practice.

However, the development process was not without its limitations. Notably, the direct involvement of patients and the public (PPI) was missing, alongside the application of qualitative research methods. This gap might affect the intervention's broader applicability and acceptance, particularly among patients. The COVID-19 pandemic imposed further constraints, limiting our capacity for broader stakeholder engagement through workshops and seminars, which could have otherwise enriched the intervention's development.

It is important to highlight there are two postal “interventions” in the study. There is the intervention which is the focus of TRAINS which is aimed at GP practices. There is also the letter template we provide to GP practices to use to send to parents/guardians of children with asthma. This letter template was based on that used in PLEASANT which had PPI to assist in its design (Boote *et al.*, 2016).

The concentration in TRAINS was an intervention aimed at GP practices. For this intervention there was extensive engagement with stakeholders who are pivotal in implementing the intervention. This engagement enabled the gathering insights from healthcare professionals, including GPs and healthcare managers, who possess the expertise and authority to enact changes in clinical practices. This focused consultation

process was thorough and time-consuming, ensuring that the intervention was shaped by those with direct influence over its practical application. While the absence of formal focus groups and lack of qualitative research represent significant omissions, the seminars conducted provided valuable, in-depth discussions, significantly informing the intervention design. This stakeholder-focused approach, deemed most suitable for achieving the immediate objectives of the TRAINS study, aimed at improving healthcare delivery through informed modifications in GP practices.

In addition to the limitations, it is important to consider the practical implications of these theoretical alignments. The HBM and TPB, while providing a robust framework for understanding behaviour change, also require careful adaptation to the specific contexts and needs of GPs. This adaptation was a key focus in our consultations and design iterations, ensuring that the final intervention was not only theoretically sound but also pragmatically relevant to the daily practices and challenges faced by GPs.

Moreover, aligning the intervention with the HBM and TPB required careful adaptation to meet GPs' specific contexts and needs. This adaptation was central to our consultations and design iterations, ensuring the final intervention was not only grounded in solid theoretical frameworks but also pragmatically aligned with the everyday realities and challenges GPs face.

4.8 Conclusion

In conclusion, the development of the intervention was a rigorous process that took six months, from November 2020 to April 2021, to produce a comprehensive and understandable resource for GPs. It involved several stages of consultations, refinements, and feedback from various stakeholders. By the end of the process, the final version of the intervention represented an effective and tailored resource for GPs, demonstrating the value of a collaborative and iterative approach to intervention design. This approach underscores the importance of stakeholder perspectives and specialist knowledge.

Throughout the development process, it is hoped that this meticulous method of development would ensure successful implementation of the intervention, contributing to the enhanced management of asthma in children and, ultimately, improved patient outcomes.

In the following chapter, we will provide an overview of the methodology used to implement this intervention into practice.

Chapter 5: Methodology

5.1 Introduction

Following the intervention detailed in the previous chapter, this chapter presents a comprehensive overview of the TRAINS study's methodology. It navigates through the study design, the use of the CPRD and the participant selection criteria. Moreover, it explains the randomisation process, the intervention delivery, the chosen outcome measures, data collection and management and the employed statistical methods.

5.2 Aims

This chapter aims to provide a clear understanding of the following key aspects:

- The scope of the TRAINS study, including its design and the role of the CPRD.
- The participant selection, encompassing the eligibility criteria and site recruitment process.
- The primary and secondary outcome measures.
- The data management protocol, the statistical techniques for data analysis, the determination of the sample size and the randomisation process.

5.3 TRAINS study

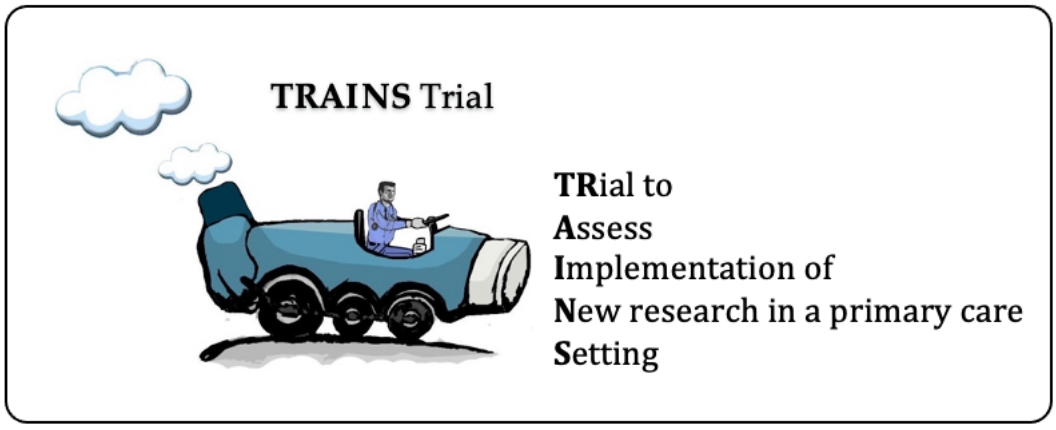


Figure 5-1 TRAINS study logo

Chapter 2 highlighted the PLEASANT trial, which found that a simple postal intervention effectively enhanced asthma outcomes for school age children with asthma in primary care settings. In Chapter 3, the use of printed educational materials, such as postal bulletins, was discussed as a strategy for disseminating research findings and influencing prescription practices. The current study, TRAINS, aimed to assess if sharing the PLEASANT trial results with GP practices would lead to an increase preventer prescriptions rate in children with asthma (Alyami *et al.*, 2022).

This approach aligns with the principles of pragmatic RCTs, which are designed to evaluate the effectiveness of interventions in real-world settings. Unlike explanatory RCTs, which test the efficacy of an intervention under ideal and controlled conditions (Schwartz and Lellouch, 1967; Thorpe *et al.*, 2009), pragmatic RCTs such as TRAINS aim to provide insights into how an intervention performs in the general population in

routine practice settings (Hotopf, 2002). These trials feature broader inclusion criteria and focus on practical outcomes, reflecting the diversity and complexities of real-world environments (Roland and Torgerson, 1998; Tunis, Stryer and Clancy, 2003).

Following the principles of pragmatic research, the TRAINS study sought to understand the real-world applicability of disseminating the PLEASANT trial outcomes to GP practices. It investigates a vital policy question: Does informing GPs about evidence-based research findings effectively alter prescription behaviour to benefit the patient population? This question is fundamental to pragmatic trials, aiming to generate knowledge that can be readily applied to improve health outcomes in the general population.

The TRAINS study's design and execution reflect the practicalities and variances inherent in everyday healthcare environments. By embracing the diversity of the healthcare landscape and focusing on actions and decisions that occur in the routine care of patients with asthma, the TRAINS trial underscores the potential for research findings to enact meaningful changes in treatment approaches and healthcare delivery when effectively communicated to healthcare providers.

5.4 Study design

In order to accurately assess the effectiveness of the intervention, a cluster-randomised controlled parallel-group trial design was employed for the TRAINS study. This design was particularly suitable as it allowed for the use of routinely collected data, thereby ensuring that the study was grounded in real-world, practical conditions (Alyami *et al.*, 2022).

The study included a total of 1,389 general practices, all participants in the CPRD Aurum database in England, as recorded in June 2021. These practices were randomised into two groups: an intervention group, comprised of 694 practices and a control group, comprised of 695 practices which continued with their usual care (refer to Figure 5.2).

This structure was chosen not only in line with the intervention's design (which was planned to be delivered at the practice level), but also for the protection it provided against contamination. This is because a cluster-randomised design minimises the risk of treatment contamination that could occur if individual patients within the same practice were assigned to different treatment groups.

Data collection, conducted via CPRD, spanned six months following the intervention's implementation, extending until December 2021.

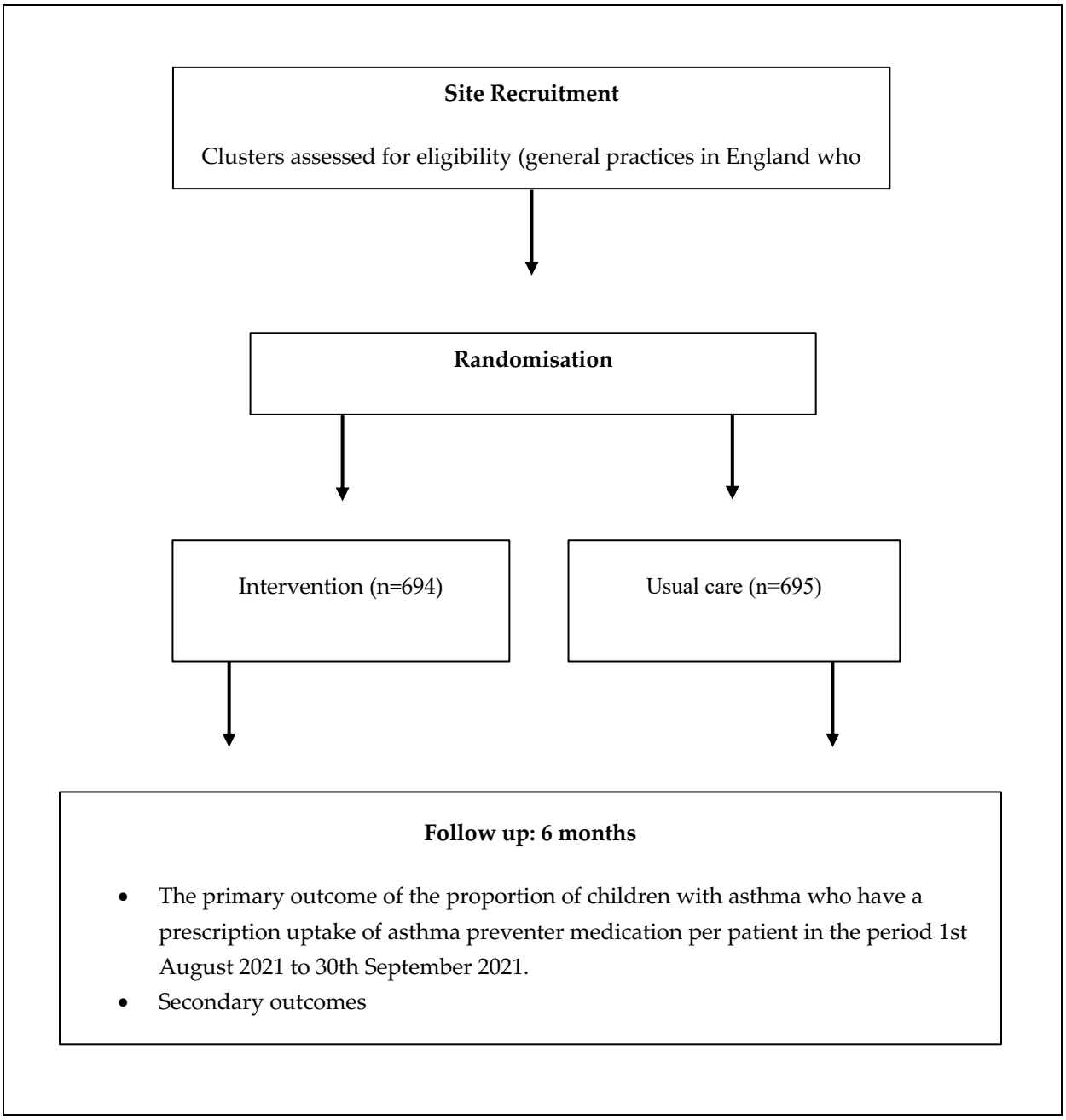


Figure 5-2 Study design

5.5 Outcome measures

The effectiveness of the intervention was evaluated through the dual analysis of prescription uptake in the period preceding the school term and subsequent medical contacts. The analysis of prescriptions uptake was divided into four time periods:

1. August to September 2021 (identified as the primary study endpoint)
2. August 2021
3. September 2021
4. July to December 2021.

The primary study endpoint, from 1 August 2021 to 30 September 2021, was considered the ideal time to observe the impact of the intervention based on the learnings from the PLEASANT trial. Furthermore, we also looked at the individual months of August and September 2021. To evaluate the long-term effects of the intervention, we assessed prescription uptake over a six months period following the intervention, from July to December 2021.

In parallel to prescription uptake, medical contacts, both unscheduled and scheduled, were analysed in the following months and window:

1. September to December 2021
2. September 2021

3. October 2021

4. November 2021

5. December 2021.

The purpose of these evaluations was to provide a comprehensive understanding of the intervention's impact on medical contact interactions during these outlined periods.

5.5.1 Primary outcome

The primary outcome measure for this trial was the proportion of children with asthma who had a prescription for an asthma preventer medication from 1st August 2021 to 30th September 2021.

5.5.2 Secondary outcome

The secondary outcome measures aimed to assess various aspects of asthma management, including prescription uptake, unscheduled medical contact, all medical contact (unscheduled and scheduled) and unscheduled medical contact associated with respiratory diagnosis. These secondary outcomes, including the respective time periods and measures used for each, are presented in Table 5.1 below.

OUTCOME MEASURES	DESCRIPTION	DATA COLLECTION PERIOD
PRIMARY OUTCOME MEASURE		
PRESCRIPTION UPTAKE	Proportion of children with asthma who have a prescription for an asthma preventer medication.	1 August 2021 to 30 September 2021
SECONDARY OUTCOME MEASURES		
1. PRESCRIPTION UPTAKE	Number of asthma preventer medication prescriptions per school-aged child with asthma.	1 August 2021 to 30 September 2021
2. PRESCRIPTION UPTAKE	Number of prescription uptakes of asthma preventer medication per patient.	August 2021
3. PRESCRIPTION UPTAKE	Number of prescription uptakes of asthma preventer medication per patient.	September 2021
4. PRESCRIPTION UPTAKE	Proportion of children with a prescription for asthma preventer medication per patient.	August 2021
5. PRESCRIPTION UPTAKE	Proportion of children with a prescription for asthma preventer medication per patient.	September 2021
6. PRESCRIPTION UPTAKE	Number of prescription uptakes of asthma preventer medication in the 6 months following the intervention.	1 July 2021 to 31 December 2021
7. UNSCHEDULED MEDICAL CONTACTS	Proportion of patients with unscheduled medical contact.	1 September 2021 to 31 December 2021 (and individual months within this period)
8. UNSCHEDULED MEDICAL CONTACTS	Number of unscheduled medical contact per patient	1 September 2021 to 31 December 2021 (and individual months within this period)
9. TOTAL MEDICAL CONTACTS	Proportion of patients with a medical contact (either unscheduled or scheduled)	1 September 2021 to 31 December 2021 (and individual months within this period)
10. TOTAL MEDICAL CONTACTS	Number of medical contact (either unscheduled or scheduled) per patient	1 September 2021 to 31 December 2021 (and individual months within this period)
11. UNSCHEDULED MEDICAL CONTACTS ASSOCIATED WITH A RESPIRATORY DIAGNOSIS	Proportion of patients with unscheduled medical contact associated with a respiratory diagnosis	1 September 2021 to 31 December 2021 (and individual months within this period)

12. UNSCHEDULED MEDICAL CONTACTS ASSOCIATED WITH A RESPIRATORY DIAGNOSIS	Number of unscheduled medical contacts per patient associated with a respiratory diagnosis	1 September 2021 to 31 December 2021 (and individual months within this period)

Table 5-1 Primary and Secondary Outcome Measures

5.6 Participants and eligibility criteria

5.6.1 Defining the target population

The target population for the intervention consisted of general practices in England that were actively contributing to the CPRD Aurum database at that time of the study in June 2021.

Data were extracted for school-aged children who had been diagnosed with asthma, were registered with an eligible practice and had received preventive prescriptions in the year leading up to the study. Detailed asthma diagnosis and preventers prescriptions codes were used to define these populations. These can be found in the Appendix F.

5.6.2 Inclusion criteria for practices:

- General practices in England that contributed to the CPRD Aurum database on or before June 2021.

5.6.3 Exclusion criteria for practices:

- General practices located outside of England.

- Practices that left CPRD post-intervention (June 2021) and before the completion of the follow-up o the primary outcome (September 2021).
- Practices that underwent a merger following the intervention and before the end of follow-up period, especially if the merged practices were initially part of different study arms.

5.6.4 Inclusion criteria for the data extraction from CPRD

- School-aged children, aged between 4 and 16 years old as of 1 September 2021, with a coded diagnosis of asthma, who had been prescribed asthma preventers medication during the past 12 months.

5.7 Allocation of preventer prescription

A comprehensive list of asthma preventer medications was developed to accurately evaluate primary and secondary outcomes. This list included a total of 421 codes, covering preventer medications prescribed to children aged 4 to 16, was the result of an extensive and methodical process.

To create this list, I undertook the following steps:

1. **PLEASANT Code List**: I began by examining the asthma preventer prescription codes used in the PLEASANT trial, based on the GP Adjudication Panel's review of the medcode descriptions.
2. **Cambridge Code List**: I then referred to the Cambridge website, which provided a reliable asthma-related drug treatment code list.
3. **CPRD Code Browser**: Both lists were alphabetically organized, and I meticulously searched each term through the CPRD code browser, ultimately combining them into one comprehensive list.
4. **Academic GP Consultation**: To further refine the list, I consulted with Dr. Phillip Oliver, a clinical lecturer in general practice. This review helped identify a few missed prescriptions related to asthma, such as prednisolone.
5. **Pharmacist Consultation**: Finally, to ensure the list was exhaustive and current, I sought the expertise of a pharmacist with extensive experience in a children's hospital. The pharmacist's review was crucial in finalizing the list, which ultimately included 421 preventers based on the CPRD code browser.

This collaborative approach, involving both academic and clinical expertise, served to enhance the accuracy, credibility and reliability of our data. The detailed process of developing this list underscores the thoroughness of our study's methodology. For a complete list of the medications, see Appendix G.

5.8 Allocation of scheduled vs. unscheduled contacts.

The classification of medical contacts as scheduled or unscheduled was informed by the consultation 'medical contacts' codes used within the GP practice's database. The process for determining whether contacts were classified as scheduled or unscheduled in this study involved several steps to ensure accuracy. Here is a detailed breakdown of the process:

1. **Initial Data Review**: The initial data came from CPRD, which contained a field called "consmedcodeid" that appeared to indicate the type of consultation that had been recorded. The first step involved mapping the codes in the "consmedcodeid" field to their corresponding medical terms. This was done by linking the codes with a medical dictionary, resulting in a list of around 70 different codes along with their associated terms.

2. Classification of Consultation Type: Each of the mapped codes was then categorized into two groups: "True medical contact" or "False medical contact." This classification was critical because only interactions falling under the "true medical contact" category would be considered for inclusion in the outcome measures of the study. To ensure the accuracy of the classification, insights from the PLEASANT study coding were used as a reference point. Additionally, further research was conducted, involving internet searches, to verify and confirm the classification of these consultation types. After the initial

classification, a meeting was scheduled with a General Practitioner (GP) who had expertise in the field. The list of classified consultation types was reviewed and confirmed by the GP, adding an extra layer of validation to the process. Any discrepancies or uncertainties in the classification were discussed and resolved during this consultation.

3. Staff Job Category Classification: In addition to consultation type, each consultation also had associated staff job categories. These staff job categories were classified as either unscheduled, scheduled, or not applicable (NA). This classification was likely done based on insights from the PLEASANT study and through further terminology research. Similar to the consultation type classification, the list of staff job categories was also reviewed and confirmed by the GP to ensure accuracy.

Scheduled contacts were thus defined as interactions that were a part of the patient's regular care schedule, like asthma reviews or repeat prescriptions.

Unscheduled contacts, on the other hand, were classified as interactions occurring outside the usual care routine, often initiated by the patient or due to acute illness.

It's important to note that while the PLEASANT study took months to complete the coding process devoted significant effort to coding, underscoring the importance of precise categorisation. Any coding errors were assumed to be equally assigned to each study arm to maintain fairness in the analysis. This detailed process helps ensure the

reliability and validity of the classification of scheduled and unscheduled contacts for the secondary outcomes. The final lists of categorised consultation types and staff job categories can be found in Appendix H.

5.9 Setting and site recruitment

The study took place within GP practices in England that were contributing to the CPRD Aurum database. As this was an implementation study, the practices did not need to consent to joining the study. Instead, they were randomly assigned to receive the intervention and it was up to them if they wanted to act upon it. Approximately 1,389 sites included in this trial, based on the number of active CPRD GP practice sites in June 2021.

5.10 Sample size

The sample size is based on feasibility and the anticipated number of practices providing data to the CPRD. We anticipate a sample size of approximately 1389 GP practices (694 on intervention and 695 on control). Alongside this, from the previous study (PLEASANT), we also anticipate 85 school-age children having asthma per practice (Julious *et al.*, 2018). Assuming an expected rate of 30% of people collecting their prescription and an intraclass correlation of 0.03, it is anticipated that the precision of the

estimates in the study—estimated as a half-width of a 95% confidence interval—will be 1%.

The rationale for the precision based approach was first influenced by the fact the sample size was based on feasibility. In addition, the primary objective of the TRAINS trial was to accurately estimate the proportion of school-aged children with asthma who collect their prescription in each group. Precision-based calculations are suited to studies trials in this context where the key interest lies in estimating a rate or a proportion with a high degree of accuracy. The study does not have a pre-specified effect size –as would be needed for a power calculation - but any effect observed is estimated accurately.

With anticipated precision of approximately 1% the hope is that the study would have reliable estimate of the prescription collection rate in the context of asthma management in school-aged children

5.11 Randomisation and allocation concealment

To ensure an equivalent sample size in each arm of the study with respect to the number of children with asthma, practices were allocated 1:1 to either intervention or control group. The randomisation process was stratified based on practice size decile within the CPRD. The included practices were identified through the CPRD and did not require prospective recruitment. GP practices assigned to the intervention group received a

postal letter and an email advising them to implement the study. In contrast, GP practices allocated to control group did not receive any postal letter or email, continued with their usual care. The process of randomisation was performed by the study statistician and then reviewed by another statistician.

5.12 The intervention

A comprehensive description of the intervention's design and elements is available in the previous chapter (refer to Chapter 4).

GP practices registered with CPRD and assigned to the intervention group received two forms of correspondence: one sent via email and another dispatched through postal mail. As this was an implementation study, the correspondence provided to the GP practices acted as a recommendation rather than an obligation. Therefore, the decision to adopt or ignore the provided recommendations was subject to the individual GP practice.

5.13 The delivery of the intervention

Our initial plan, as outlined in the previous chapter, was to deliver the intervention in May and June. However, due to a delay in receiving the ISAC approval, we were only able to send the intervention in June. It was sent via email on 23 June 2021 and through postal on 25 June 2021, all of which was facilitated by the CPRD. A total of 694 postal packs were dispatched promptly via First Class post and emails were successfully

delivered to 694 GP practices. When possible, more than one email contact per practice was used, including the practice manager and the lead GP, resulting in 1403 contacts being emailed. A read receipt was requested from the CPRD for the emails. The letter was sent to the CPRD contact lead at GP practices and was addressed to the practice manager and the asthma lead. Given the timing of the intervention, it was anticipated that GP practices would deliver their corresponding communications to parents during the school holidays, providing enough time to implement the advice offered by the intervention.

5.14 Data source

5.14.1 Clinical Practice Research Datalink

The TRAINS study used data from the CPRD. The CPRD is a database of medical records from general practices that updated regularly to serve as a significant resource for healthcare research. With information on over 39 million individuals, including 13 million active records that meet quality standards, the CPRD represents approximately 20% of the UK population and accurately reflects age, gender and ethnicity (CPRD, 2022).

CPRD uses medical coding systems, like Read codes, for the standardised recording of patient data. This approach to data collection, which prefers codes over free text, improves both the consistency and searchability of the information (Herrett *et al.*, 2015).

However, this method might limit the comprehensiveness and specificity detail of the collected data.

The CPRD database is a rich source of patient information, such as symptoms, test results, diagnoses and demographic data (CPRD, 2022). It presents a cost-effective alternative to primary data collection, significantly reducing both financial and time constraints for studies (Khan, Harrison and Rose, 2010).. As the data is anonymised and collected by GP practices, the need for individual patient ethics approvals is not required (CPRD, 2022). While patients have the option to opt out, practices participate in the data collection process on a voluntary basis.

With its comprehensive coverage, including follow-up data, enables studies to investigate long-term outcomes and make more precise epidemiological associations. The Quality and Outcomes Framework, an incentivized program, has enhanced data quality by encouraging GPs to record key items like smoking status (Herrett *et al.*, 2015). Additionally, the potential for data linkage with other healthcare datasets allows for a more comprehensive examination of patient care pathways and outcomes (Herrett *et al.*, 2015).

However, there are challenges associated with using CPRD data. The accuracy and quality of the data can be variable, as it is entered during GP consultations and not primarily for research purposes. GPs have a wide range of diagnosis codes to choose

from, and practices may vary in their coding routines (Khan, Harrison and Rose, 2010). These discrepancies can affect the reliability and validity of studies using CPRD data, emphasising the need for careful selection of clinical codes to ensure accurate research outcomes (Williams *et al.*, 2012). Also, this variability can lead to under coding or missing certain patient issues. Although CPRD has methods to assess data quality, these do not guarantee perfect data (Herrett *et al.*, 2015). Missing data is another concern, as certain outcomes may not be consistently recorded. Additionally, specific populations like private patients, homeless individuals, and those in residential homes may not be fully represented in the database (Herrett *et al.*, 2015).

It should be noted that for TRAINS the primary outcome is collection of medication. These data do have limitations. From PLEASANT the fact a prescription was collected – and the type of medication - was easy to determine but the posology of the prescriptions to calculate the medicine procession ratio (MPR) was not possible (Julious *et al.*, 2016). In TRAINS also collection of prescription was easy to determine.

In summary, the CPRD database offers extensive potential for healthcare research, but researchers must be mindful of nuances in data quality and representation. This understanding is crucial for designing accurate studies, interpreting data, and drawing valid conclusions.

5.15 Data collection

The CPRD extracted all eligible records from the May 2022 CPRD Aurum database build. These records included patients aged 4 to 16 years as of 1st September 2021, registered with GP practices in England that were involved in the TRAINS study. To qualify, patients must have had an asthma diagnosis and a prescription for an asthma medication in the past year from 1st June 2020 and 31st May 2021, implying active asthma. Also, they had to be alive as of the primary analysis period's end on 30st September 2021.

The extracted data included all medical contacts, including prescription requests and out-of-hours contacts. CPRD provided anonymised data for each patient, encompassing factors such as the General Practice identifier, year and month of birth (for patients under 16), sex, ethnic group, details of any asthma medication prescribed along with the date and medical contact data for each appointment, including the date. The research team only had access to fully anonymised data, ensuring no access to any patient identifiable information.

5.16 Data handling

The Data Management Team (DMT) at ScHARR handled the task of processing and preparing the data for statistical analysis. The process involved reformatting data initially recorded on an individual basis, which included consultations, observations, referrals,

issues and prescriptions. The DMT consequently generated two distinct analysis datasets, one for prescription and the other for medical contacts. Each row in these datasets represented either a prescription uptake or a medical contact.

The details of data handling and quality assurance was outlined in a data management plan. All data processing was methodically carried out using the R programming language for consistent and reliable analysis and Git software was employed for script management. All data processing activities were documented to maintain transparency and traceability in our methodology. More details can be found in the TRAINS data processing file in the Appendix I.

5.17 Statistical methods

Appropriate statistical methods for a cluster randomised trial were conducted in the data analysis, with the reporting adhering to the CONSORT guidelines for Cluster RCTs (Campbell *et al.*, 2012). Although we anticipated possible changes such as mergers, closures, or splits in some practices. Even though a small number of practices might have undergone such changes, we did not require any special procedures and we had no plans for any data imputation.

Statistical significance was assessed at a two-sided significance level of 5% and all analyses adhered to this level. The construction of data was carried out using SPSS

(version 28), Stata (version 17) was used for the analyses and R (version 4.2.3) was utilised for creating time series plots.

5.17.1 Analysis populations

We performed the primary analyses of effectiveness on the intention-to-treat (ITT) population, comprising all practices from which we collected data during the study period. We also conducted sensitivity analyses on email read receipt (RR), which represented a subset of practices in the ITT analysis, as identified by read receipt email confirmations.

5.17.2 Estimands Framework

Estimated Treatment Effect: The study adopts the participant-average treatment effect as the estimand, focusing on the individual-level impact of informing GPs about the PLEASANT trial results. This approach is in line with the research question: "Does informing GPs of the results from the PLEASANT trial prevent the drop in prescription uptake in school-aged children with asthma during the summer holidays?" (ICH, 1998; Rubin, 2005).

Population (Target of Estimation): The estimand targets the population of school-aged children (aged 4 to 16) with an asthma diagnosis in participating GP practices within the CPRD.

Treatment Conditions (Intervention and Comparator): The intervention involves sending a letter to GPs who are part of the CPRD, informing them about the PLEASANT trial results with recommendations. The comparator is standard routine practice without this intervention.

Outcome (Variable of Interest): The primary outcome is the proportion of children who have a prescription uptake for asthma preventer medication during the summer holidays, measured as a binary variable (prescription uptake: yes/no).

Handling of Intercurrent Events: Strategies to address intercurrent events that could affect the outcome, such as dropping out from the CPRD during the study period, will be integral to the analysis. These events will be documented, and their potential impact on the outcome will be assessed.

Population-Level Summary Measure: The analysis will utilise odds ratios to compare prescription uptake rates between the intervention and control groups. This measure will help quantify the effect of the intervention at the individual child level. Refer to Section 5.17.3 for further details.

Statistical Analysis Approach: Consistent with the participant-average treatment effect, a mixed-effects logistic regression model will be employed to analyse the primary outcome data. This model accounts for the clustering of patients within GP practices and

includes fixed effects for key covariates (e.g., age, gender, ethnicity) and the intervention. The model's random effects will capture variations across GP practices. Refer to Section 5.17.3 for further details.

The selection of the participant-average treatment effect as the estimand is justified by its direct relevance to the individual-level impact of the intervention. This reflects the study's aim to assess the effect on each child's prescription uptake.

5.17.3 Statistical analysis

5.17.3.1 Demographics and baseline characteristics

Baseline characteristics of practices and patients were gathered and compared between the intervention and control groups. At the subject level, we provided descriptive statistics for gender, age group, ethnicity (in terms of frequencies and percentages) and age (in terms of mean, SD, median, IQR, minimum and maximum). At the practice level, we reported the IMD deciles (frequencies and percentages) and the number of children per practice (mean, median, IQR, range, SD, minimum and maximum).

5.17.3.2 Random effect

In the TRAINS study, we employ random effects to effectively handle the inherent variability within our study's nested data structure. This section clarifies the purpose and

role of random effects and explores the multilevel organisation of our study's data, underscoring its importance in guiding the selection of these effects.

Multilevel Data Structure in the TRAINS Study

The data within the TRAINS study is hierarchically organised, constituting two levels of analysis:

Level 2 (Practice Level): Practices are individually identified by GP ID. This allows for the modelling of variation in outcomes attributable to specific practice-related factors.

Level 1 (Individual Level): The base level of analysis focuses on individual subjects—children with asthma.

Fixed Effects include:

- **Allocation (Intervention Grouping):** Represents the assignment of GP practices to either the intervention (letter) or control group. This variable is crucial for assessing the effect of the intervention on prescription uptake rates.
- **Gender:** Categorised as male vs. female, included to evaluate any differential impact of the intervention across genders.
- **Age Group:** Divided into three categories (<5 years, 5 to 11 years, and >12 years), allowing for the analysis of age-specific effects on prescription uptake.

- **Ethnicity:** Included to assess the role of ethnic background in influencing prescription uptake.
- **Prescription Uptake in August 2019:** Serves as a baseline measure for comparing prescription uptake rates pre Covid-19.
- **Prescription Uptake in August 2020:** Another baseline measure to evaluate changes in prescription uptake rates during Covid-19.
- **Practice Size (Deciles):** GP practices categorised by deciles representing the practice size are considered as a fixed effect to reflect how the size of the practice influences the outcomes.
- **Index of Multiple Deprivation scores (IMD):** Including the IMD as a fixed effect, reduce the variability in the outcome variable that can be attributed to deprivation.

Understanding this multilevel structure is crucial. It recognises that patient outcomes are influenced by more than just individual factors; they are also shaped by the healthcare practice's environment and the wider socioeconomic circumstances.

Random Effects in the TRAINS Study

In the detailed analysis of the TRAINS study, the inclusion of GP ID as random effects was aimed to address the inherent complexities of analysing healthcare data. This

approach is designed to account for the multilevel nature of the data, recognising that patients are nested within GP practices, which exhibit unique operational characteristics.

Inclusion of GP ID: Including GP ID as a random effect allows the model to account for the clustering effect within GP practices. This recognises that patient outcomes within a specific practice are likely to be more similar to each other than to outcomes from patients in other practices due to shared practice-specific characteristics, such as practice culture, efficiency, and the specific healthcare professionals involved. Having GP ID as a random effects enables the model to accommodate the intra-cluster correlation and the complex interaction between patient-level and practice-level factors.

The decision to model GP ID as random effects was informed by a comprehensive understanding of the data structure and the specific objectives of the TRAINS study. It reflects a nuanced approach to modelling healthcare data, emphasising the importance of capturing the real-world variability and complexity inherent in patient outcomes across different GP practices.

5.17.3.3 Choice of statistical model

For the statistical analysis of cluster randomised controlled trials (cRCTs), a variety of models can be employed, including the Generalized Linear Models (GLM) estimated through Generalized Estimating Equations (GEE). Nonetheless, this study has chosen the

Multilevel Mixed-Effect Model, commonly referred to as the random effect model, due to its compatibility with our design and research aims.

This choice is motivated by the model's capacity to adeptly manage the hierarchical data inherent in cRCTs. Specifically, in the TRAINS study, the structure involves four distinct levels: individual patients at Level 1, grouped within GP practices at Level 2. The multilevel mixed-effect model excels in managing such complexity by incorporating random effects to address the intra-cluster correlation seen in cRCTs, thereby ensuring the accuracy of treatment effect estimates across the data hierarchy.

Although GEE is effective for computing population-averaged effects and shows resilience to certain misspecifications, it falls short in estimating random effects. In contrast, the multilevel mixed-effect model enriches our analysis by revealing the variability within the data, offering a deeper comprehension of its intrinsic structure.

Therefore, the selection of the multilevel mixed-effect model for our analysis aligns more closely with the nuanced research questions posed by our cRCT and the intricate nature of our data structure. This model's proficiency in delivering detailed insights across the data's multilevel hierarchy distinctly positions it as the preferred choice over GEE for the aims of this study.

5.17.3.4 Covariates

We included specific covariates such as gender, age group, ethnicity, 2019 and 2020 baselines, and the trial arm (intervention or control) within our statistical model due to their potential prognostic importance in relation to asthma management and prescription patterns. This decision was also influenced by the methodology of the PLEASANT study, which provided a precedent for considering these factors in similar research contexts.

1. Trial Arm (Intervention or Control): Differentiating between the intervention and control groups is crucial to evaluate the effectiveness of the intervention. This covariate allows for a direct comparison of outcomes, elucidating the intervention's impact.

2. Gender: Gender is included as a covariate due to its known impact on asthma prevalence and response to treatment. Differences in asthma symptoms and medication efficacy between genders can significantly influence outcomes and are thus crucial for a comprehensive analysis.

3. Age Group: Age is a fundamental factor in asthma treatment and management. Different age groups have varied responses to asthma medication and exhibit different disease characteristics, making age a vital covariate to consider in our models.

4. Ethnicity: Ethnicity is linked to variations in asthma prevalence, severity, and medication usage. Including ethnicity as a covariate helps in understanding the diverse

impacts of asthma across different ethnic groups, which is essential for addressing healthcare disparities.

5. 2019 and 2020 Baselines: These years serve as reference points to assess temporal changes in asthma management. The inclusion of two baselines was particularly strategic. The year 2019 provides a pre-pandemic baseline, offering insights into typical asthma management trends unaffected by the COVID-19 pandemic. The year 2020, in contrast, offers a baseline within the pandemic context, allowing us to account for the extraordinary impact of the pandemic on healthcare practices, including asthma prescription patterns. This dual baseline approach enables a comprehensive analysis of the intervention's effects against a backdrop of significant global health disruption.

We used binary coding for outcomes like prescription uptake or unscheduled contacts, where each child was coded '1' for occurrence and '0' for non-occurrence in those years. For count outcomes like the number of prescriptions, these baselines were recorded as numeric counts. This coding strategy allowed us to comprehensively analyse changes and trends over time, assessing the impact of the intervention on asthma management.

6. Practice Size (Deciles): Practice size deciles are Including as fixed effects in the model, independent of other covariates. This enhances the interpretability of the model by accounting for the influence of practice size on outcomes. Understanding the impact of practice size is crucial, as it can significantly affect healthcare delivery and patient

outcomes. Larger practices may have more resources and staff, potentially resulting in different care approaches compared to smaller practices.

7. Index of Multiple Deprivation scores (IMD): Including the IMD as a fixed effect in the random effects model helps to improve the control of confounding variables, enhance the interpretability of the model, and provide more efficient and accurate estimates of the effects of interest.

By including these covariates, our aim was to conduct a comprehensive analysis that accounts for the multifaceted factors influencing asthma prescription practices and medical contacts outcomes. Furthermore, the inclusion of dual baseline years enriches our investigation, offering insights into how the extraordinary circumstances of 2020 may have altered the landscape of asthma management. This methodological choice not only mirrors the approach taken in the PLEASANT study but also ensures our findings are robust, relevant, and reflective of the complexities of managing asthma in real-world settings.

5.17.3.5 Primary outcome analysis

Mixed-effect logistic regression was used to analyse the proportion of children having a prescription uptake within the primary time period. This approach was chosen due to its suitability for analysing binary outcomes. The model incorporated covariates such as

gender, age group, ethnicity and 2019 and 2020 baseline and the trial arm (intervention or control) as fixed effects. Additionally, the cluster effect of general practice and its deprivation (IMD) was included as a random effect to account for clustering within practices. This allowed us to estimate odds ratios (OR) and 95% confidence intervals (CIs).

5.17.3.6 Secondary outcome analysis

The secondary outcome analysis followed a similar approach to the primary analysis. This involved assessing the proportion of children having a prescription or medical contacts (scheduled or unscheduled) within each time period.

The number of prescriptions uptake made by the children in each period, the number of unscheduled medical contacts, and the number of total medical contacts within a given time period were analysed using a mixed-effects negative binomial model, which is suitable for dealing with count data. Negative binomial regression was chosen over Poisson regression because it assumes that each individual may have a different rate. This model allowed the estimation of incidence rate ratios (IRR) and 95% confidence intervals (CIs), while considering the same covariates as before.

5.17.3.7 Subgroup analysis

In this study, we conducted exploratory subgroup analyses to evaluate the impact of our intervention across different demographic groups, specifically focusing on sex, age group, and ethnicity. Importantly, we did not rely on p-values in our analysis or tests for interaction. Instead, we focused on point estimates and confidence intervals (CIs) to explore potential differences in the intervention's impact.

We applied separate models for each subgroup, using mixed-effect logistic regression for binary data and the negative binomial model for count data. We consistently included the same covariates in these models as appropriate. This methodological choice aimed to identify potential variations in the intervention's response among different subgroups. The results were presented in forest plots to provide a clear and descriptive visual representation of the allocation estimates for each individual subgroup analysis.

Despite multiple confidence intervals, we did not adjust for multiple testing. Instead, we focused on identifying trends rather than establishing statistical significance. This approach requires us to interpret the results carefully and to acknowledge that calculating many confidence intervals is a limitation of our study.

Thus, the subgroup analyses were undertaken to offer preliminary insights into the heterogeneity of treatment effects to enhance the understanding of the intervention's impact across different demographic groups and to guide recommendations for further work as appropriate.

5.18 Ethical approval

This trial received ethical approval from the University of Sheffield Research Ethics Committee (Reference Number: 037412) on 26 April 2021, following a submission on 8 December 2020. Additionally, an Independent Scientific Advisory Committee (ISAC) approval was granted for Clinical Practice Research Datalink (CPRD) database research (Protocol Reference ID: 21_000436) on 16 June 2021, after a submission on 15 April 2021. It is important to note that the ISAC approval was delayed due to the impact of the COVID-19 pandemic. During this period, COVID-19-related research was prioritised and fast-tracked within the CPRD, causing other approvals to be postponed (see https://cprd.com/approved-studies-using-cprd-data). Despite the delay, these approvals ensured that the trial adhered to ethical guidelines and maintained the highest standards of research conduct. The ethical approval can be found in Appendix J.

5.19 Funding

This trial has been funded by Saudi Cultural Bureau in the UK (SACB) and Jazan University, Saudi Arabia.

5.20 Summary

The TRAINS study was a pragmatic cluster randomised implementation trial using routine data from CPRD. This implementation study targeted general practices in England contributing to the CPRD Aurum database as of June 2021. A total of 1389 GP practices in England were included in the trial; 694 GP practices were randomised to the intervention group and 695 control group of usual care.

The intervention was a letter to GPs informing them of the PLEASANT study findings with recommendations. Initially, the plan was to send the intervention in May 2021 via email and in June 2021 by postal mail. However, due to the delay in obtaining the ISAC approval, CPRD sent the intervention only in June 2021 by postal and email and obtained all data for the study, including prescription and medical contacts data.

Analyses were conducted on an ITT basis with additional sensitivity analyses was carried out on RR. Also, we discussed the use of mixed-effect logistic regression and negative binomial models in the statistical analysis.

In the next chapter, the findings of the TRAINS study will be presented. It will include the participant flow process, detailing the number of participants involved and a comprehensive analysis of measured outcomes, covering primary and secondary outcomes. Additionally, it will involve a sensitivity analysis of the read receipt data and subgroup analyses.

Chapter 6: TRAINS Results

6.1 Introduction

The previous chapter described the methodology of the TRAINS study. This chapter presents the results of the study. The first section provides a detailed account of the participants flow process, the number of participants and the analysis of the outcomes measured, including primary and secondary objectives. The second section presents a sensitivity analysis of the read receipt data and subgroup analyses.

6.2 Aims

The aim of this chapter is to achieve the following:

- To report the participants' process and numbers in the TRAINS.
- To present the analysis results for the primary and secondary outcomes.
- To present sensitivity analysis of the read receipt data.
- To present the subgroup analyses

6.3 Participant flow

This study was undertaken with 1389 general practices derived from the CPRD Aurum database in England, where 694 GPs were randomised to the intervention (letter) group and 695 to the control group.

Initial data from the CPRD suggested that the May 2022 Aurum build comprised 1,491. However, this number was refined by a series of exclusions, as detailed in the table below:

Practices Excluded	**Number of Practices**	**Reason for Exclusion**
Initial exclusion	102	Practices not included in the randomisation file
Duplicate identifier	2	Unclear which records were accurate due to duplicated identifier
No longer in database	1	Practice no longer presents in the Aurum database
No asthma diagnosis	1	Data restricted to individuals with asthma diagnosis
No medication prescription	27	No prescribed asthma medication from June 2020 to May 2021
Not registered pre-intervention	1	Patients not registered with the practice before August 2021
Left pre-study	7	Patients who left the practice before August 2021
Last data collection pre-intervention	24	Patients whose last data collection was before August 2021
Total Exclusions	**165**	

Table 6-1 Breakdown of practices

Following these exclusions, the final cohort consisted of 1,326 practices with 90,583 individuals. Out of these, 664 practices (44,708 individuals) were assigned to the intervention group, while 662 practices (45,875 individuals) to the control group. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram, illustrated in Figure 6.1, outlines participant progression throughout the trial and reasons for exclusion.

6.4 Number of patients and analysis subset

The number of patients and practices were assessed for each study period based on the available dataset specific to each respective timeframe. Only those practices consistently submitting data for the entirety of each period were included in the analysis for that period.

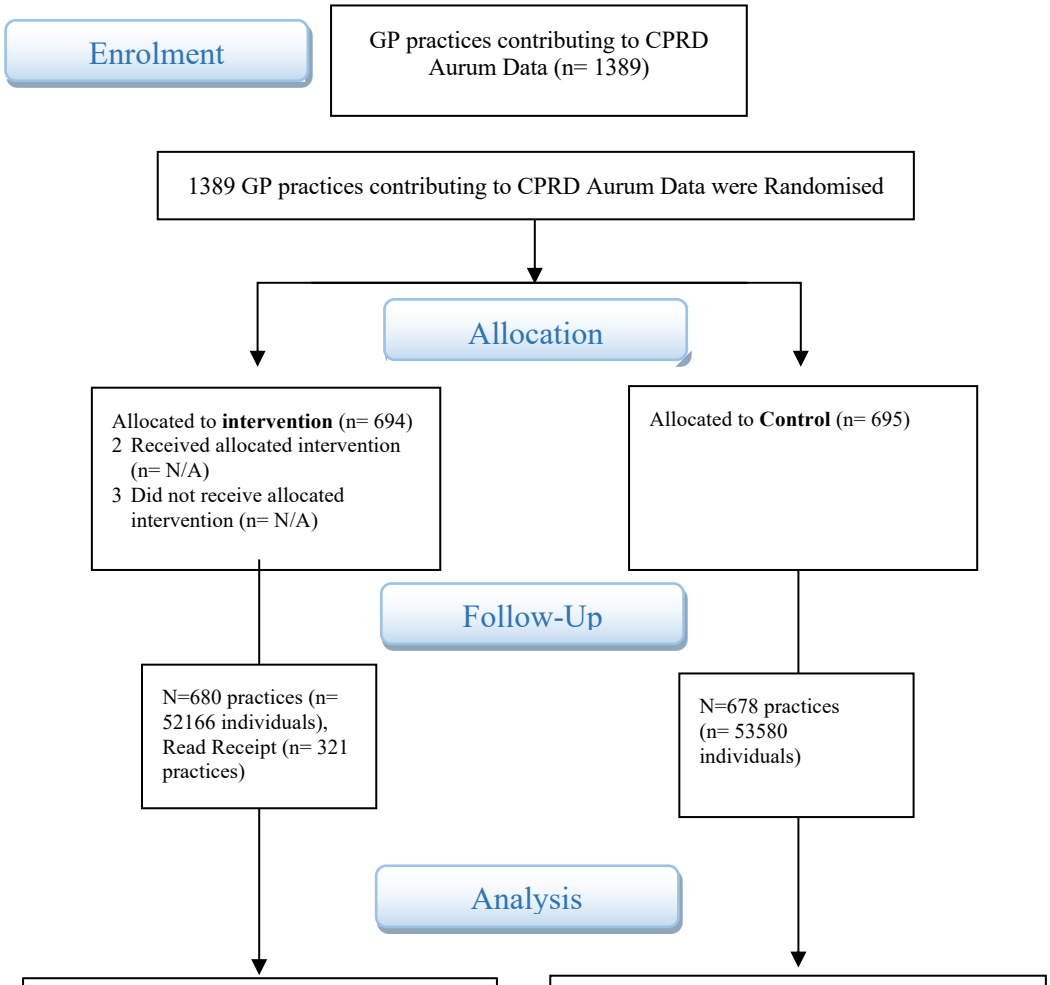
To provide a clearer illustration, practices that stopped data contribution to the CPRD before the end of the follow-up period were excluded from the corresponding analysis of that period. However, they were not excluded retrospectively. Their data was included in the analyses of the preceding periods, until their final point of data contribution.

For example, if a practice stopped contributing data in November 2021. This practice's data up until November would still be included in the analyses for all preceding periods, but not for the periods following November.

Similarly, patients who were registered at the practices before the intervention time period were included in the analysis. If a patient left a practice or if their last data collection occurred before the end of a follow-up period, they were excluded from the corresponding analysis of that period. However, they were included in the analyses of the preceding periods until their final point of data contribution.

This approach ensures that the analysis for each time period accurately reflects the dataset specific to that period, without being influenced by subsequent changes in the practices or patient population.

Figure 6.1 in the CONSORT flow diagram illustrates the number of patients and practices considered in the statistical analysis for each time period and the reasons for exclusion. The diagram is designed to provide a clear visual representation of the progression of participants through each period of the trial and the resulting changes in the analysis subsets over time.



Lost to follow-up (n= 31 practices)
- Removing one duplicate practice id, and one that was no longer in Aurum database (n= 2)
- Limiting the data to only children in the timeframe of interest. (n= 1)
- Limiting the data to only children with a diagnosis of interest. (n= 1)
- Limiting the data to only children who have been prescribed an asthma medication in the past 12 months (2020-06-01 to 2021-05-31). (n= 26)
- One practice id had been duplicated and was removed from the data as it was not possible to distinguish which records were correct. (n= 1).

Analysed (n= 664 practices, n= 44708 individuals)
Read Receipt (RR) (n= 302 practices)

		ITT	RR
Prescription uptake	Aug – Sep 21	N_P=663 P_I=44465 P_O=243	N_P=301 P_I=20663 P_O=23802
	Aug 21	N_P=664 P_I=44708 P_O=0	N_P=302 P_I=20778 P_O=23930
	Sep 21	N_P=663 P_I=44465 P_O=243	N_P=301 P_I=20663 P_O=23802
	July – Dec 21	N_P=659 P_I=43747 P_O=961	N_P=300 P_I=20296 P_O=24412
Medical contacts	Sep 21	N_P=663 P_I=44465 P_O=243	N_P=301 P_I=20663 P_O=23802
	Oct 21	N_P=660 P_I=44064 P_O=644	N_P=300 P_I=20440 P_O=23624
	Nov 21	N_P=660 P_I=43887 P_O=821	N_P=300 P_I=20352 P_O=23535
	Dec 21	N_P=659 P_I=43747 P_O=961	N_P=300 P_I=20296 P_O=23451
	Sep – Dec 21	N_P=659 P_I=43747 P_O=961	N_P=300 P_I=20296 P_O=23451

Analysed (n = 662 practices, n= 45875 individuals)

		ITT	RR
Prescription uptake	Aug – Sep 21	N_P=661 P_I=45559 P_O=316	N_P=661 P_I=45559 P_O=316
	Aug 21	N_P=662 P_I=45875 P_O=0	N_P=662 P_I=45875 P_O=0
	Sep 21	N_P=663 P_I=45559 P_O=243	N_P=663 P_I=45559 P_O=243
	July – Dec 21	N_P=659 P_I=45013 P_O=862	N_P=659 P_I=45013 P_O=862
Medical contacts	Sep 21	N_P=661 P_I=45559 P_O=316	N_P=661 P_I=45559 P_O=316
	Oct 21	N_P=659 P_I=45310 P_O=565	N_P=659 P_I=45310 P_O=565
	Nov 21	N_P=659 P_I=45154 P_O=721	N_P=659 P_I=45154 P_O=721
	Dec 21	N_P=659 P_I=45013 P_O=862	N_P=659 P_I=45013 P_O=862
	Sep – Dec 21	N_P=659 P_I=45013 P_O=862	N_P=659 P_I=45013 P_O=862

Excluded (n= 32 practices, n= 15161 individuals)

- Limiting data to only patients who register before Aug 21 (n= 1 practice, n= 2621 individuals)
- Removing patients who left practices before Aug 21 (n= 7 practice, n= 3736 individuals)
- Removing patients who last data collection before Aug 21 (n= 24 practice, n= 650 individuals)
- Removing missing data from age variable (n= 0 practice, n= 8154 individuals)

Figure 6-1 Shows the CONSORT flow diagram. (RR= Read receipt, NP = Number of practices, PI= Patients in analysis, and P0=Patient out of analysis compared to Aug 21)

6.5 Baseline characteristics

The intervention (letter) group and the control group were similar in terms of average age, gender distribution and ethnicity. The mean age of the included patients was 10.08 (SD 3.18), with an age range of 4 to 15 years. Among the children with asthma included in the study, 60% were male and 40% were female. Additionally, the majority of the patients identified as white (61%). There was a minor difference in the distribution of practices and patients, with 664 practices (44,708 patients) in the letter (intervention) arm and 662 practices (45,875 patients) in the control arm. Descriptive statistics for patients and practices within both the intervention and control groups are illustrated in Table 6.2, while Figure 6.2 shows the count of patients per practice size decile within each group.

(A) At subject level, descriptive statistics of gender, age group and ethnicity (frequencies and percentages) and age (mean, SD, median, IQR, minimum and maximum).

Variable		Control (n=45875)	Letter (n=44708)	Total (n= 90583)
Gender	Male, n (%)	27,600 (60%)	26,785 (60%)	54,385 (60%)
	Female, n (%)	18,275 (40%)	17,925 (40%)	36,200 (40%)
Age	Minimum	4	4	4
	Median (IQR)	10.0 (8.0-13.0)	10.0 (8.0-13.0)	10.0 (8.0-13.0)
	Mean (SD)	10.1 (3.18)	10.1 (3.18)	10.1 (3.18)
	Maximum	15	15	15
Age group	< 5, n (%)	1,855 (4%)	1,900 (4%)	3,755 (4%)
	5 to 11, n (%)	26,635 (58%)	26,225 (59%)	52,860 (58%)
	> 11, n (%)	17,385 (38%)	16,585 (37%)	33,970 (38%)
Ethnicity	Asian or Asian British, n (%)	5,745 (13%)	5,700 (13%)	11,445 (13%)
	Black, Black British, Caribbean or African, n (%)	2,765 (6.0%)	2,350 (5%)	5,115 (6%)
	Mixed or multiple ethnic groups, n (%)	2,060 (5%)	1,830 (4%)	3,890 (4%)
	White, n (%)	2,7630 (60%)	27,455 (61%)	55,085 (61%)
	Other ethnic group, n (%)	860 (2%)	745 (2%)	1,605 (2%)
	NR, n (%)	6815 (15%)	6,630 (15%)	13,445 (15%)
Baseline: The proportion of children who had a prescription	August-September 2020, n (%)	18,375 (40.1%)	17,792 (39.8%)	36,167 (39.9%)
	August-September 2019, n (%)	15,061 (32.8%)	14,756 (33.0%)	29,817 (32.9%)

(B) At practice level, descriptive statistics of Practice size deciles, IMD (frequencies and percentages) and number of children per practice (mean, median, IQR, range, SD, minimum and maximum)

Variable		Control (n=662)	Letter (n=664)	Total (n= 1326)
Practice Size	1, n (%)	64 (9.7%)	62 (9.3%)	126 (9.5%)
	2, n (%)	65 (9.8%)	65 (9.8%)	130 (9.8%)
	3, n (%)	63 (9.5%)	67 (10.1%)	130 (9.8%)
	4, n (%)	71 (10.7)	69 (10.4%)	140 (10.6%)
	5, n (%)	66 (10.0%)	69 (10.4%)	135 (10.2%)
	6, n (%)	66 (10.0%)	67 (10.1%)	133 (10.0%)
	7, n (%)	67 (10.1%)	65 (9.8%)	132 (10.0%)
	8, n (%)	64 (9.7%)	64 (9.6%)	128 (9.7%)
	9, n (%)	71 (10.7%)	72 (10.8%)	143 (10.8%)
	10, n (%)	65 (9.8%)	64 (9.6%)	129 (9.7%)
IMD	1, n (%)	48 (7.3%)	41 (6.2%)	89 (6.7%)
	2, n (%)	46 (6.9%)	61 (9.2%)	107 (8.1%)
	3, n (%)	59 (8.9%)	49 (7.4%)	108 (8.1%)
	4, n (%)	53 (8.0%)	51 (7.7%)	104 (7.8%)
	5, n (%)	74 (11.2%)	64 (9.6%)	138 (10.4%)

	6, n (%)	72 (10.9%)	69 (10.4%)	141 (10.6%)
	7, n (%)	73 (11.0%)	66 (9.9%)	139 (10.5%)
	8, n (%)	72 (10.9%)	76 (11.4%)	148 (11.2%)
	9, n (%)	74 (11.2%)	94 (14.2%)	168 (12.7%)
	10, n (%)	91 (13.7%)	93 (14.0%)	184 (13.9%)
Number of children per practice	Minimum	1	1	1
	Median (IQR)	57 (37-87)	58 (37-89)	58 (38-88)
	Mean (SD)	69 (52)	67 (47)	68 (49)
	Maximum	620	388	620

Table 6-2 Descriptive statistics at the individuals and practices levels.

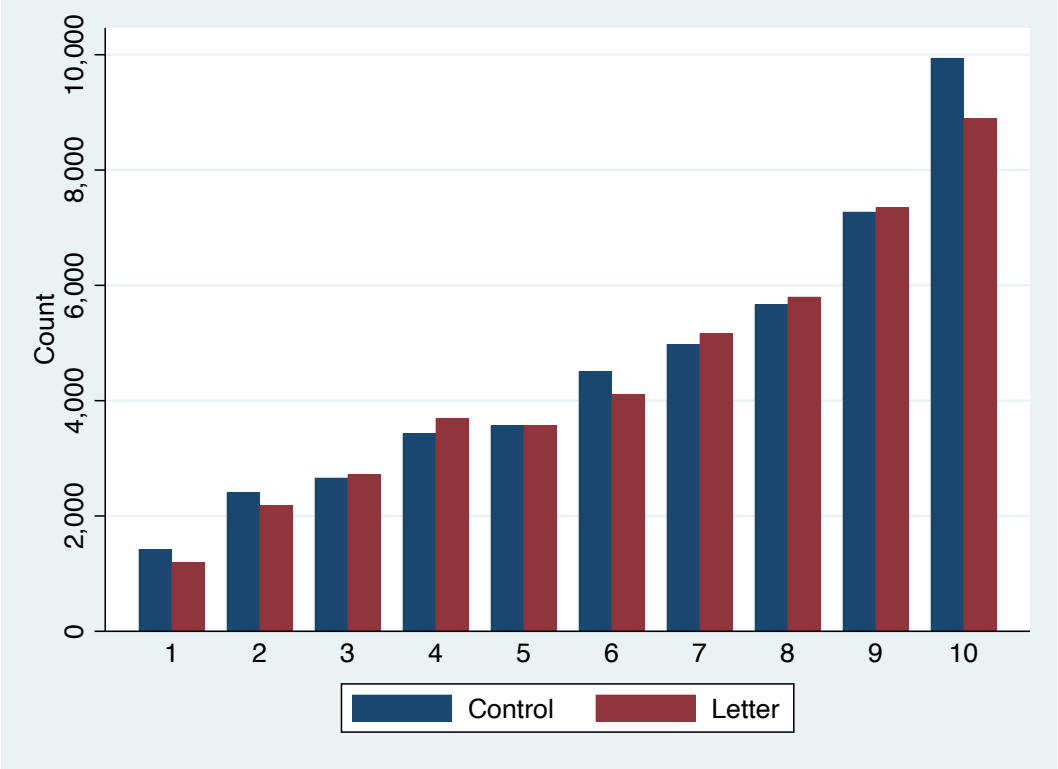


Figure 6-2 Shows the number of patients per practice size deciles.

6.6 Primary outcome:

6.6.1 The proportion of children with asthma who have a prescription for an asthma preventer medication from 1 August 2021 to 30 September 2021.

The results of the multilevel mixed-effect model for the primary outcome, which is the proportion of children who filled a prescription in August and September 2021. The primary outcome analysis findings are presented in table 6.3.

The analysis included data from a total of 90,024 patients across 1,324 practices, divided into two groups: Intervention and Control. In the Intervention group, consisting of 44,465 patients from 663 practices, 15,716 children (35.3%) picked up a prescription during the specified period. In the Control group, with 45,559 patients from 661 practices, 16,001 children (35.1%) picked up a prescription.

After adjusting for covariates such as gender, age group, ethnicity, baseline data from 2019 and 2020, IMD, and practice size, the analysis showed an adjusted odds ratio of 1.01 for the Intervention group compared to the Control group. This odds ratio, with a 95% confidence interval (CI) of 0.97 to 1.04, suggests that there was no statistically significant difference in the likelihood of children picking up a prescription between the two groups during August and September 2021.

proportion of children who have a prescription in Aug and Sep 21.

Independent variables	No of Patients / Practices	Events (%)	Adjusted odds ratio	(95% Confidence interval)
Allocation				
Intervention	44,465/663	15716 (35.3%)	1.01	(0.97 -1.04)
Control	45,559/661	16,001 (35.1%)		

Table 6-3 Mixed-effects logistic regression results with random effect for the proportion of children who have a prescription in Aug and Sep 21.

The ICC for the primary outcome model was 0.009.

6.7 Secondary outcomes:

6.7.1 Prescription uptake

To assess the effect of the letter on prescriptions uptake, we also analysed the number of prescription uptake in various periods: August 2021, September 2021, from 1 August 2021 to 30 September 2021 and over the 6 months following the intervention, starting from 1 July 2021 to 31 December. Figure 6.3 illustrates the monthly prescriptions uptake by children during the study period.

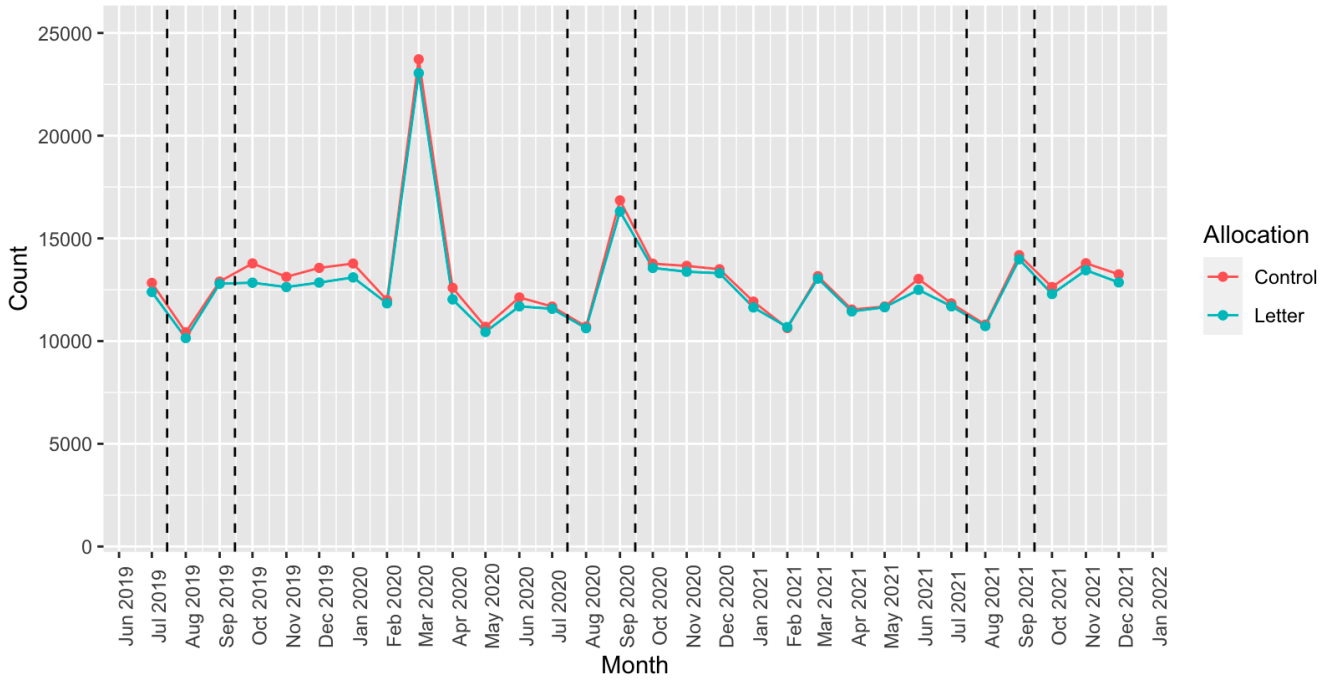


Figure 6-3 Number of prescriptions picked up by children each month

Figure 6.3 illustrates the number of preventer prescriptions collected by the children, split by allocation. It indicates no difference between the two groups regarding the number of prescriptions uptake from August to September 2021. Interestingly, in March 2020, the number of preventers prescription uptakes nearly doubled during the COVID-19 period. Additionally, the graph still exhibits a consistent annual decline in August each year.

6.7.1.1 The proportion of children who have a prescription for asthma preventer medication per patient.

The study assessed whether the children picked up a prescription on the individual months of August and September 2021. The results of the mixed-effect logistic regression for proportion of children who have prescriptions in August and September 2021 are presented in Table 6.4. The odds ratios (ORs) for August and September 21 were 1.01 (95% CI: .96 to 1.05) and 1.01 (95% CI: .97 to 1.06), respectively. These findings suggest that there was no statistically significant difference in allocation between the arms.

Time Period	Intervention		Control		Adjusted Odds Ratio	95% CI
	Children with a Prescription	Total Pts/Prac	Children with a Prescription	Total Pts/Prac		
Aug - Sep '21	15,716 (35.3%)	44,465/663	16,001 (35.1%)	45,559/661	1.01	0.97 to 1.05
Aug '21	8,330 (18.6%)	44,708/664	8,475 (18.5%)	45,875/662	1.01	0.96 to 1.05
Sep '21	10,972 (24.7%)	44,465/663	11,139 (24.5%)	45,559/661	1.01	0.97 to 1.05

Table 6-4 Mixed logistic regression with random effect results for the proportion of children who have a prescription in August 2021 and September 21. (Pts = patients, Prac = practices)

6.7.1.2 The number of prescription uptake of asthma preventer medication per patient.

The analysis involved assessing the incidence rate ratios (IRR) and their corresponding 95% confidence intervals (CI) for the number of prescription uptakes in different time periods. In terms of allocation, the IRR for the letter group in August 21 was 1.02 (95% CI: 0.98, 1.06) and this ratio remained relatively consistent across subsequent time periods, including September, August to September and July to December 2021. These findings indicate that there was no statistically significant difference in the incidence rates of prescription uptake between the letter and control groups during these periods. Please refer to Table 6.5 for a summary of the results.

Time Period	Intervention		Control		Incidence Ratio	95% CI
	Mean (SD)	Total Pts/Prac	Mean (SD)	Total Pts/Prac		
Aug - Sep '21	0.55 (0.95)	44,465/663	0.55 (0.93)	45,559/661	1.01	0.98 to 1.03
Aug '21	0.24 (0.56)	44,708/664	0.24 (0.55)	45,875/662	1.02	0.98 to 1.05
Sep '21	0.31 (0.62)	44,465/663	0.31 (0.61)	45,559/661	1.01	0.98 to 1.04
Jul - Dec '21	1.69 (2.45)	43,747/659	1.68 (2.43)	45,013/659	1.00	0.98 to 1.02

Table 6-5 Mixed-effects negative binomial regression with random effect for the number of prescription uptake per patient at different time.

6.7.2 Unscheduled Medical Contacts (UMC)

Given that the study aimed to increase preventer prescriptions in children with asthma during the summer, therefore it is relevant to investigate unscheduled contacts by children after returning back to school in the period from September to December 2021. In this section of the findings, we present the analysis of unscheduled medical contacts in different time periods. Figure 6.4 displays a plot of the counts of monthly unscheduled contacts made by the children during the study period.

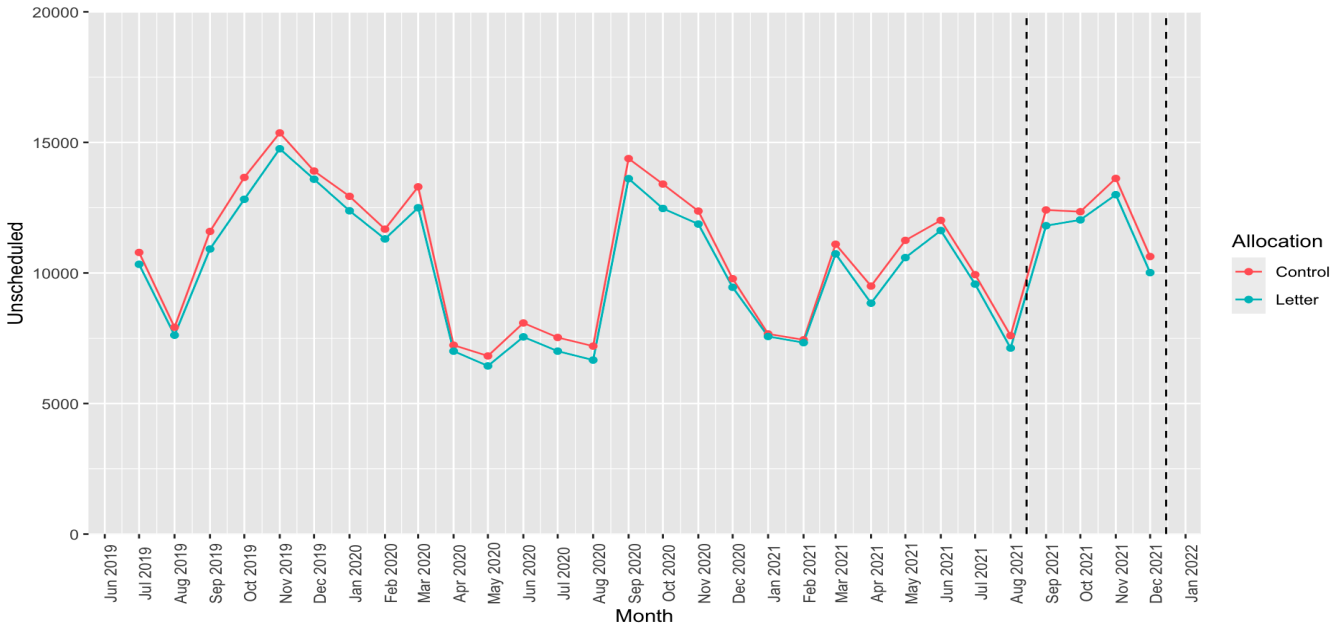


Figure 6-4 Time series plot for unscheduled medical contacts by children by allocation.

Figure 6.4 is a time series plot of the number of unscheduled contacts made by the children each month within the study timeframe. It shows the peaks and troughs in the dataset for unscheduled medical contacts and indicates no substantial difference between

the intervention and control arms during the timeframe from September to December 2021. Notably, our analysis still demonstrates the recurring "September peak" observed in each year during the study frame. Furthermore, there is a noticeable dip in the number of unscheduled contacts from March 2020 to August 2020 due to the implementation of lockdown measures, followed by a subsequent spike in September coinciding with the return to schools.

6.7.2.1 The proportion of patients with unscheduled medical contact from 1 September 2021 to 31 December 2021 and the individual months of 1 September 2021 to 31 December 2021.

A mixed-effect logistic regression model was used to assess the proportion of patients with unscheduled medical contact for various time period endpoints. The results indicate that the allocation variable did not demonstrate statistical significance across any of the five models. Specifically, the ORs for the months of September, October, November, December and September to December 2021 were 1.00 (95% CI: .95 to 1.06), 1.02 (95% CI:.96, 1.09), .99 (95% CI: .93 to 1.05), .98 (95% CI: .92 to 1.04) and 0.99 (95% CI: .92 to 1.06), respectively. See table 6.6 for more details.

Time Period	Intervention		Control		Adjusted Odds Ratio	95% CI
	Children with UMC	Total Pts/Prac	Children with UMC	Total Pts/Prac		
Sep '21	7,837 (17.6%)	44,465/663	8,276 (18.2%)	45,559/661	0.98	0.93 to 1.03
Oct '21	8,066 (18.3%)	44,064/660	8.371 (18.5%)	45,310/659	0.99	0.94 to 1.04
Nov '21	8,596 (19.6%)	43,887/660	9,014 (20.0%)	45,154/659	0.97	0.93 to 1.02
Dec '21	6,878 (15.7%)	43,747/659	7,286 (16.2%)	45,013/659	0.96	0.91 to 1.01
Sep - Dec '21	20,369 (46.6%)	43,747/659	21,435 (47.6%)	45,013/659	0.97	0.92 to 1.01

Table 6-6 Mixed-effect logistic regression with random effect results for the proportion of patients who have unscheduled contacts at different time.

6.7.2.2 The number of unscheduled medical contact per patient from 1 September 2021 to 31 December 2021 and the individual months from 1 September 2021 to 31 December 2021

A mixed-effect negative binomial model with random effect was used to assess the number unscheduled medical contacts that children had within different time periods. Table 6.7 presents the analysis results, which revealed the allocation was not statistically significant in any of the five models, with IRR ranging from 0.98 to 1.03 and 95% confidence intervals including unity. The results are consistent with the findings from prescription uptake.

Time Period	Intervention		Control		Incidence Ratio	95% CI
	Mean (SD)	Total Pts/Prac	Mean (SD)	Total Pts/Prac		
Sep '21	0.24 (0.60)	44,465/663	0.25 (0.60)	45,559/661	0.98	0.94 to 1.03
Oct '21	0.25 (0.61)	44,064/660	0.25 (0.60)	45,310/659	1.00	0.96 to 1.05
Nov '21	0.27 (0.64)	43,887/660	0.27 (0.64)	45,154/659	0.99	0.95 to 1.03
Dec '21	0.21 (0.56)	43,747/659	0.22 (0.56)	45,013/659	0.96	0.91 to 1.01
Sep - Dec '21	0.97 (1.49)	43,747/659	0.98 (1.49)	45,013/659	0.99	0.96 to 1.02

Table 6-7 Mixed-effects negative binomial regression with random effect for the number of unscheduled contacts per patient at various times.

6.7.3 All Medical Contacts (AMC): (scheduled and unscheduled)

This part presents the analysis of the medical contacts, including scheduled and unscheduled. The number of all medical contacts made by the children each month during the study period is presented in Figure 6.5. This figure is a time series plot that shows peaks and troughs in the medical contacts.

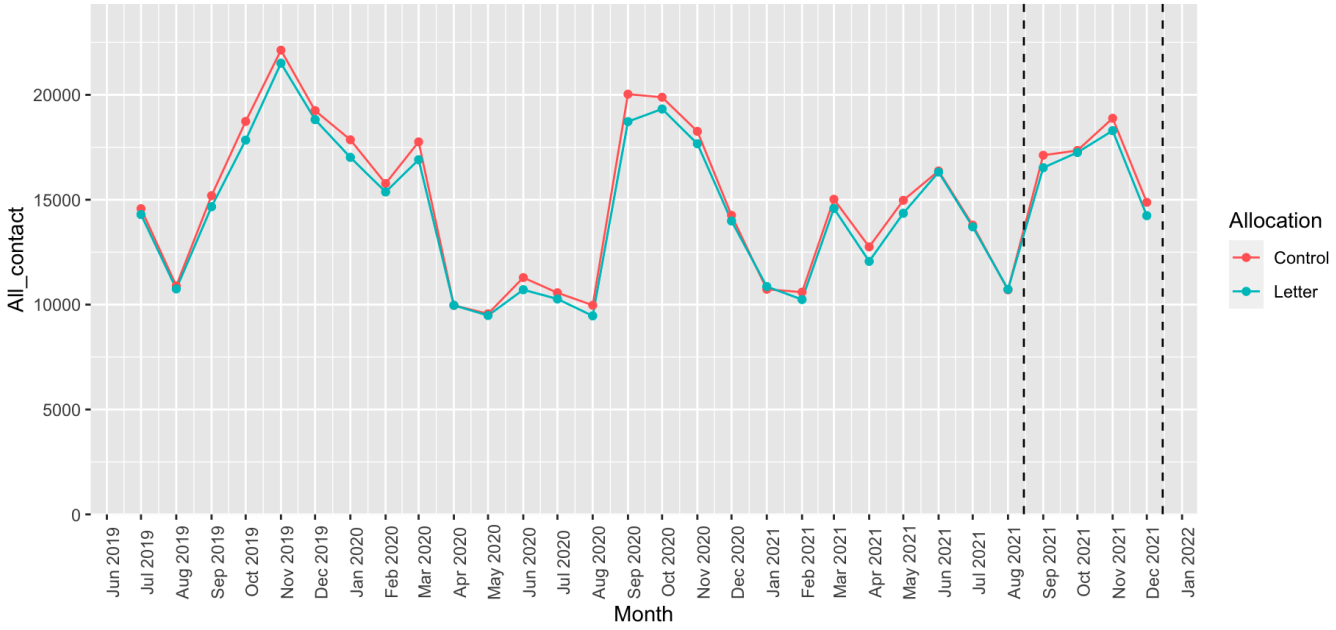


Figure 6-5 Time series plot for all medical contacts by children

Figure 6.5 shows all medical contacts made by children each month during the study period, including scheduled or unscheduled contacts. It is consistent with Figure 6.4 and demonstrates no difference between the intervention and control groups from September to December 2021.

6.7.3.1 The proportion of patients with a medical contact (either unscheduled or scheduled) from 1 September 2021 to 31 December 2021 and the individual months from 1 September 2021 to 31 December 2021

The mixed-effect logistic model was used to evaluate the proportion of children with medical contact who had a contact at different time periods. Our analysis of the allocation revealed an OR of 1.00 (95% CI: 0.92, 1.03) during September 2021. This ratio remained stable throughout, October, November, December and the September-December 2021 period, indicating no statistically significant difference in odds between letter and control groups. A summary of the findings is displayed in Table 6.8.

Time Period	Intervention		Control		Adjusted Odds Ratio	95% CI
	Children with AMC	Total Pts/Prac	Children with AMC	Total Pts/Prac		
Sep '21	11,190 (25.2%)	44,465/663	11,560 (25.4%)	45,559/661	1.00	0.95 to 1.05
Oct '21	11,678 (26.5%)	44,064/660	11,951 (26.4%)	45,310/659	1.00	0.96 to 1.05
Nov '21	12,195 (27.8%)	43,887/660	12,759 (28.3%)	45,154/659	0.99	0.94 to 1.03
Dec '21	9,858 (22.5%)	43,747/659	10,362 (23.0%)	45,013/659	0.97	0.93 to 1.02
Sep - Dec '21	26,653 (60.9%)	43,747/659	27,749 (61.6%)	45,013/659	0.99	0.94 to 1.04

Table 6-8 Mixed-effect logistic regression with random effect results for the proportion of patients with any medical contacts across different points in time.

6.7.3.2 The total number of medical contact (either unscheduled or scheduled) per patient in the period 1 September 2021 to 31 December 2021 and the individual months of 1 September 2021 to 31 December 2021.

To assess the number of medical contacts that children had within different time frames, we used a mixed-effect negative binomial model with random effect. Table 6.9 presents the results of this analysis which indicate no statistically significant difference in incidence rates between the intervention group and control group during September 2021, with an IRR of 1.00 (95% CI: 0.95, 1.03). This ratio remained relatively constant in October, November, December and the September-December 2021 period, suggesting no statistically significant difference in incidence rates between allocation groups during these periods as well.

Time Period	Intervention		Control		Incidence Ratio	95% CI
	Mean (SD)	Total Pts/Prac	Mean (SD)	Total Pts/Prac		
Sep '21	0.37 (0.77)	44,465/663	0.38 (0.77)	45,559/661	0.99	0.95 to 1.03
Oct '21	0.39 (0.79)	44,064/660	0.38 (0.76)	45,310/659	1.01	0.97 to 1.05
Nov '21	0.42 (0.82)	43,887/660	0.42 (0.81)	45,154/659	1.00	0.96 to 1.03
Dec '21	0.33 (0.72)	43,747/659	0.33 (0.72)	45,013/659	0.98	0.94 to 1.02
Sep - Dec '21	1.50 (1.95)	43,747/659	1.51 (1.91)	45,013/659	1.00	0.97 to 1.02

Table 6-9 Mixed-effect negative binomial regression with random effect for the number of any medical contact per patient at various time points.

6.7.4 Unscheduled medical contact in associated with a respiratory diagnosis

Unfortunately, the analysis for this section could not be performed as the required information regarding respiratory diagnoses from the DMT was not derivable within the time interval of the study, as their involvement in the project had concluded. Consequently, this portion of the project, which includes two secondary outcomes, remains unfinished:

1- **The proportion of patients who have an unscheduled medical contact in the period 1 September 2021 to 31 December 2021 and the individual months of 1 September 2021 to 31 December 2021 associated with a respiratory diagnosis**
2- **The number of unscheduled medical contacts per patient and from 1 September 2021 to 31 December 2021 and the individual months of 1 September 2021 to 31 December 2021 associated with a respiratory diagnosis**

6.8 Sensitivity analysis

6.8.1 Read receipt

The letter was sent by postal and email to reach out to 695 practices using CPRD, with 664 practices ultimately included in the analysis, as clarified in the participant flow section. As part of our effort to track engagement, we were able to get the email read receipt feature provided by CPRD, which allowed us to know if our email was opened by the CPRD contact lead at the practice. Figure 6.6 shows the email open rates among the intervention group.

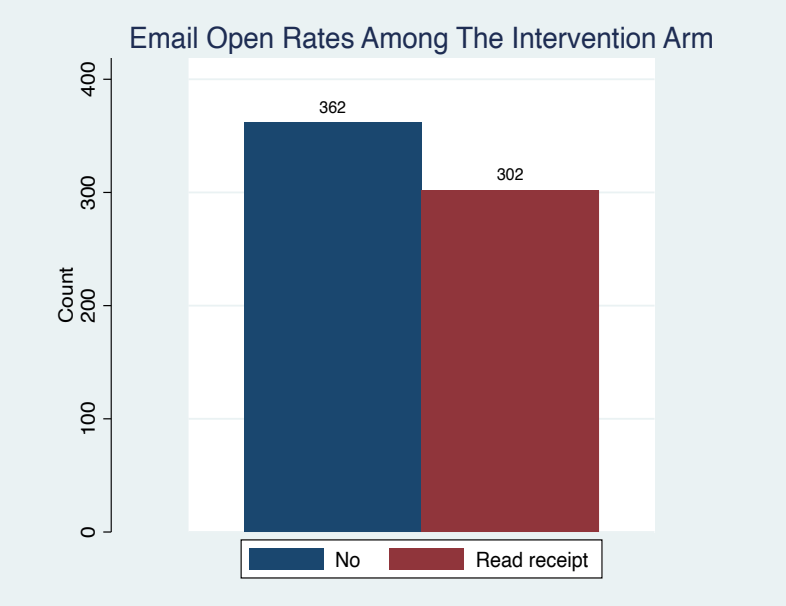


Figure 6-6 Comparison of email open rates among the intervention group

After the intervention period was over, we received read receipts from 302 (45.5%) of the 664 contacted practices, while the remaining 362 (54.5%) did not provide read receipts or respond at all. These notifications helped us to analyse the practices that opened our email in comparison to the control group.

6.8.1.1 Prescription uptake

6.8.1.1.1 The proportion of children with asthma who have a prescription for an asthma preventer medication in August, September and from 1 August to 30 September 2021.

We utilised a mixed-effect logistic regression to analyse the proportion of children with asthma who picked up a preventer prescription in August, September and August-September 2021 period. Our findings show an OR of 1.03 (95% CI: 0.98, 1.08) during August-September 2021 (the primary outcome). This ratio remained stable throughout the individual months of August and September 2021, indicating no statistically significant difference in incidence rates between groups. Please refer to Table 6.4 for a summary of the results.

Time Period	Intervention		Control		Adjusted Odds Ratio	95% CI
	Children with a Prescription	Total Pts/Prac	Children with a Prescription	Total Pts/Prac		
Aug - Sep '21	7,423 (35.9%)	20,663/301	16,001 (35.1%)	45,559/661	1.02	0.98 to 1.07
Aug '21	3,924 (18.9%)	20,778/302	8,475 (18.5%)	45,875/662	1.02	0.96 to 1.08
Sep '21	5,209 (25.2%)	20,663/301	11,139 (24.5%)	45,559/661	1.02	0.97 to 1.08

Table 6-10 Mixed-effect logistic regression with random effect results for the proportion of children who have a prescription at different time

6.8.1.1.2 The number of prescription uptake of asthma preventer medication per patient.

We used the mixed-effect negative binomial regression model for different time period endpoints. In August 21, the IRR for the letter arm was 1.03 (95% CI: 0.99, 1.08), which remained consistent in September, August-September and July-December 2021 time period. Based on these findings, there were no statistically significant differences between the letter and control groups in terms of incidence rates. However, the effects are bigger for read receipt compared to the ITT analysis. Please refer to Table 6.11

Time Period	Read Receipt		Control		Incidence Ratio	95% CI
	Mean (SD)	Total Pts/Prac	Mean (SD)	Total Pts/Prac		
Aug - Sep '21	0.56 (0.95)	20,663/301	0.55 (0.93)	45,559/661	1.02	0.98 to 1.05
Aug '21	0.25 (0.57)	20,778/302	0.24 (0.55)	45,875/662	1.03	0.98 to 1.08
Sep '21	0.32 (0.61)	20,663/301	0.31 (0.61)	45,559/661	1.01	0.97 to 1.05
Jul - Dec '21	1.72 (2.49)	20,296/300	1.68 (2.43)	45,013/659	1.01	0.99 to 1.04

Table 6-11 Mixed-effects negative binomial regression with random effect for the number of prescription uptake per patient at different time.

6.8.1.2 Unscheduled medical contacts

6.8.1.2.1 The proportion of patients with unscheduled medical contact from 1 September 2021 to 31 December 2021 and the individual months of 1 September 2021 to 31 December 2021.

In Table 6.12, the results of the mixed-effects logistic regression model for various time periods are presented. There was no statistical significance associated with the allocation variable across all five models. In particular, the odds ratios for September, October, November, December and September to December 2021 were 1.02 (95% CI: .95 to 1.20), 1.04 (95% CI: .97, 1.12), 1.00 (95% CI: .93 to 1.07), 0.99 (95% CI: .92 to 1.07) and 0.98 (95% CI: .90 to 1.07), respectively.

Time Period	Read Receipt		Control		Adjusted Odds Ratio	95% CI
	Children with UMC	Total Pts/Prac	Children with UMC	Total Pts/Prac		
Sep '21	3,734 (18.1%)	20,663/301	8,276 (18.2%)	45,559/661	1.01	0.95 to 1.08
Oct '21	3,878 (19.0%)	20,440/300	8.371 (18.5%)	45,310/659	1.02	0.96 to 1.09
Nov '21	4,082 (20.1%)	20,352/300	9,014 (20.0%)	45,154/659	1.00	0.94 to 1.07
Dec '21	3,276 (16.1%)	20,296/300	7,286 (16.2%)	45,013/659	0.99	0.93 to 1.06
Sep - Dec '21	9,633 (47.5%)	20,296/300	21,435 (47.6%)	45,013/659	1.00	0.94 to 1.06

Table 6-12 Mixed-effect logistic regression with random effect results for the proportion of patients who have unscheduled contacts at different time.

6.8.1.2.2 The number of unscheduled medical contact per patient from 1 September 2021 to 31 December 2021 and the individual months from 1 September 2021 to 31 December 2021

Table 6.13 shows mixed-effect negative binomial models to estimate the number of unscheduled medical contacts children had over different time periods. The results of this analysis showed that the allocation was not statistically significant in any of the five models, with IRRs ranging from 0.98 to 1.06 and 95% confidence intervals included the value of 1.

Time Period	Read Receipt		Control		Incidence Ratio	95% CI
	Mean (SD)	Total Pts/Prac	Mean (SD)	Total Pts/Prac		
Sep '21	0.25 (0.60)	20,663/301	0.25 (0.60)	45,559/661	1.02	0.96 to 1.08
Oct '21	0.26 (0.61)	20,440/300	0.25 (0.60)	45,310/659	1.03	0.97 to 1.09
Nov '21	0.27 (0.63)	20,352/300	0.27 (0.64)	45,154/659	1.00	0.95 to 1.06
Dec '21	0.21 (0.56)	20,296/300	0.22(0.56)	45,013/659	0.98	0.92 to 1.04
Sep - Dec '21	0.99 (1.49)	20,296/300	0.98 (1.49)	45,013/659	1.01	0.97 to 1.05

Table 6-13 Mixed-effects negative binomial regression with random effect for the number of unscheduled contacts per patient at various times.

6.8.1.3 All medical contacts (scheduled and unscheduled)

6.8.1.3.1 The proportion of patients with a medical contact (either unscheduled or scheduled) from 1 September 2021 to 31 December 2021 and the individual months from 1 September 2021 to 31 December 2021

As shown in Table 6.14, the mixed-effect logistic model results of the proportion of children who had a medical contact during different timeframes. From September to December, including the entire September-December period, the OR of 1.03 (95% CI: 0.97, 1.10) for the allocation (letter) remained stable, indicating that there was no significant variation in the odds ratio between the intervention and control groups.

Time Period	Read Receipt		Control		Adjusted Odds Ratio	95% CI
	Children with AMC	Total Pts/Prac	Children with AMC	Total Pts/Prac		
Sep '21	5,326 (25.8%)	20,663/301	11,560 (25.4%)	45,559/661	1.03	0.97 to 1.09
Oct '21	5,536 (27.1%)	20,440/300	11,951 (26.4%)	45,310/659	1.02	0.96 to 1.08
Nov '21	5,679 (27.9%)	20,352/300	12,759 (28.3%)	45,154/659	0.99	0.94 to 1.05
Dec '21	4,627 (22.8%)	20,296/300	10,362 (23.0%)	45,013/659	0.98	0.92 to 1.04
Sep - Dec '21	12,423 (61.2%)	20,296/300	27,749 (61.6%)	45,013/659	1.00	0.94 to 1.06

Table 6-14 Mixed-effect logistic regression with random effect results at different time for the proportion of patients with any medical contacts across different points in time.

6.8.1.3.2 The total number of medical contact (either unscheduled or scheduled) per patient in the period 1 September 2021 to 31 December 2021 and the individual months of 1 September 2021 to 31 December 2021.

The findings of this analysis are presented in Table 6.15, which show that there is no significant difference in incidence rates between the intervention and control groups for September 2021, with an IRR of 1.02 (95% CI: 0.97, 1.07). This IRR was consistent in October, November, December and the September-December 2021 period, indicating that there was no substantial variation in incidence rates across allocation variables throughout these months as well.

Time Period	Read Receipt		Control		Incidence Ratio	95% CI
	Mean (SD)	Total Pts/Prac	Mean (SD)	Total Pts/Prac		
Sep '21	0.38 (0.79)	20,663/301	0.38 (0.77)	45,559/661	1.02	0.97 to 1.07
Oct '21	0.40 (0.80)	20,440/300	0.38 (0.76)	45,310/659	1.03	0.98 to 1.08
Nov '21	0.42 (0.83)	20,352/300	0.42 (0.81)	45,154/659	1.00	0.95 to 1.04
Dec '21	0.33 (0.74)	20,296/300	0.33 (0.72)	45,013/659	0.98	0.93 to 1.04
Sep - Dec '21	1.54 (2.00)	20,296/300	1.51 (1.91)	45,013/659	1.01	0.97 to 1.04

Table 6-15 Mixed-effects negative binomial regression with random effect for the number of unscheduled medical contact per patient at various time points.

6.9 Subgroup analysis

In this section of analysis, we conducted comprehensive subgroup analyses to investigate the effects of our intervention on specific demographic groups. Subgroups and labels used in the analysis include:

- Sex: Male, Female
- Age: <5, 5 to 11, 12+
- Ethnicity: Asian or Asian British, Black or Black British, Caribbean or African, Mixed or multiple ethnic groups, White, Other ethnic group, Not reported (NR)
- IMD Level: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10

The primary aim of these subgroup analyses was to assess the impact of the intervention within each of these distinct population groups, while accounting for the other variables that were included in the model. We focused on investigating prescriptions in August-September 2021, unscheduled contacts from September-December 2021 and all medical contacts within the same timeframe.

To present the results in a clear and descriptive manner, we utilised forest plots. These plots allow for a visual representation of the allocation effect estimates for each individual subgroup analysis, all on the same forest plot. This approach provides a more detailed

understanding of how the intervention's effects vary across the diverse demographic subgroups, highlighting any notable patterns or differences.

By conducting these subgroup analyses and presenting the findings in forest plots, we aimed to gain valuable insights into the intervention's effectiveness within specific population segments. This analysis further enhances the overall understanding of the study's outcomes and informs potential variations in the impact of the intervention across different demographic categories.

6.9.1 Prescription uptake in August and September 2021

6.9.1.1 The proportion of children with asthma who have a preventer prescription.

The subgroup analysis using mixed-effect logistic regression examined factors such as sex, age group, ethnicity and IMD for the proportion of children with asthma who have a preventer prescription during August-September 2021. The odds ratios (ORs) for all subgroups were close to 1, with the 95% confidence intervals including 1, indicating no statistically significant differences in prescription rates based on sex, age group, or ethnicity. However, some variation was noted within IMD levels, with categories 8 and 9 showing slightly elevated ORs (1.12 and 1.17, respectively), though only these categories suggested a possible increase in prescriptions. Overall, these factors did not significantly affect the prescription of asthma preventer medication in the period studied. The results of the logistic regression are further visually represented in the forest plot (see Figure 6.7).

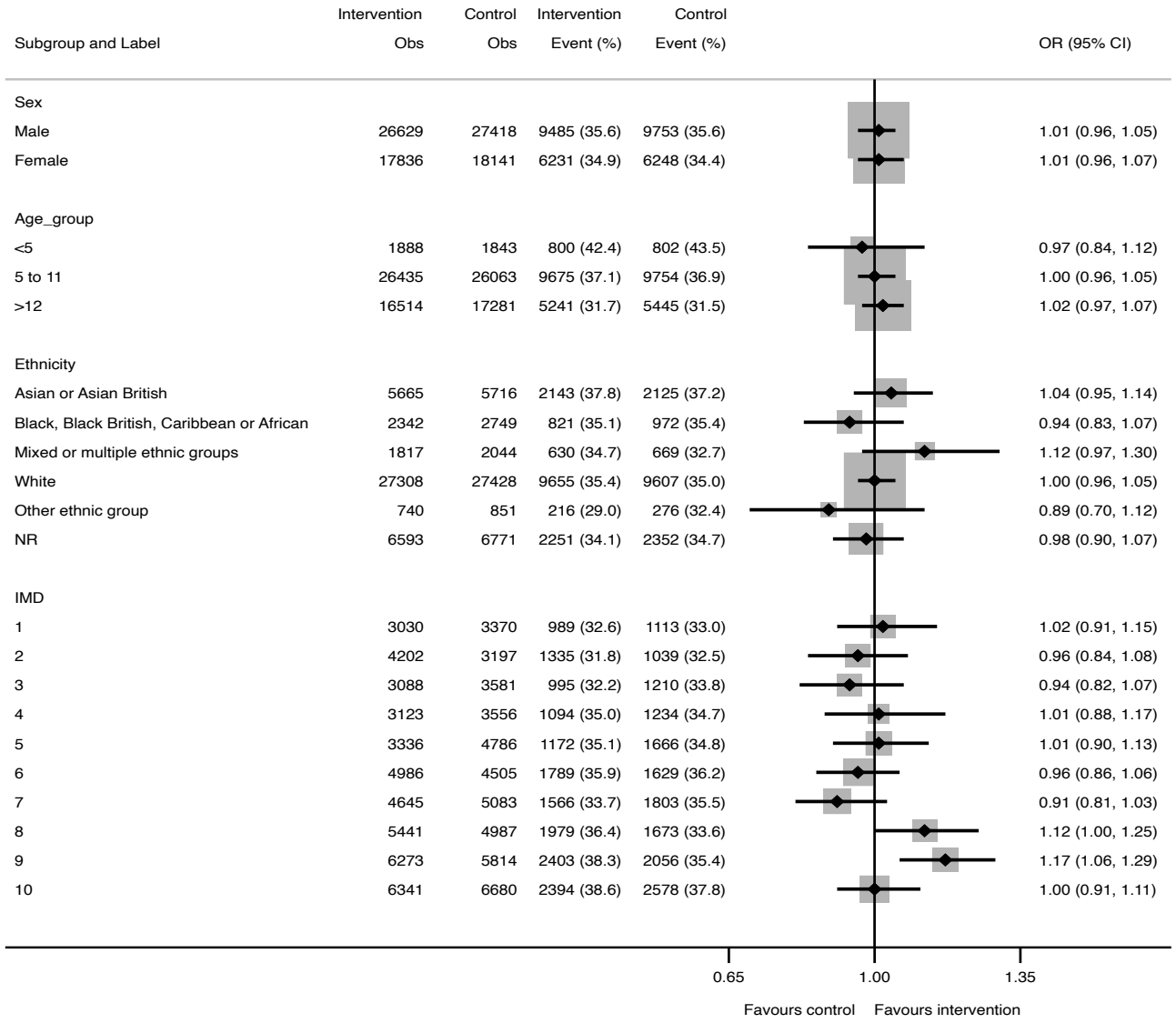


Figure 6-7 Forest plot of mixed-effect logistic regression analysis for the allocation estimates of prescription (August – September 2021) within each subgroup analyses.

6.9.1.2 The number of prescription uptake of asthma preventer medication per patient.

The mixed-effect negative binomial regression analysis assessed the number of prescription uptakes of asthma preventer medication per patient from August to September 2021. The incident rate ratios (IRR) for subgroups based on sex, age, and ethnicity were mostly close to 1, with the 95% confidence intervals including 1, suggesting no statistically significant in prescription frequencies across these demographics. Notably, within the Index of Multiple Deprivation (IMD) categories, there was some variation, with categories 8 and 9 showing IRRs of 1.08 and 1.06, respectively, indicating a slightly higher prescription rates, although only marginally so. Overall, the data suggest minimal impact of the analysed demographic factors on prescription uptake rates, with the detailed results presented in the associated forest plot (refer to Figure 6.8).

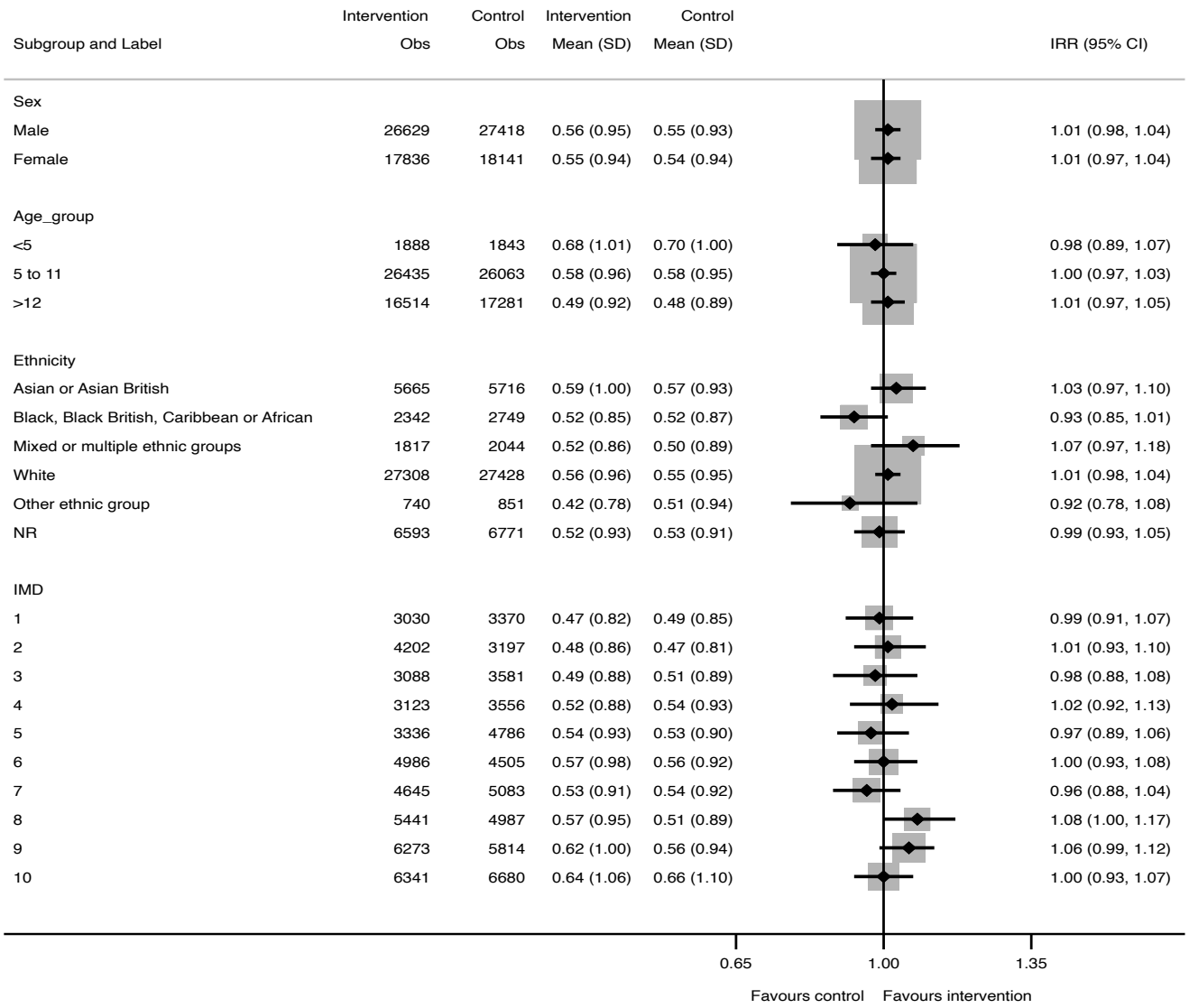


Figure 6-8 Forest plot of mixed-effect negative binomial regression analysis for the allocation estimates of prescription (September-December 2021) within each subgroup analyses.

6.9.2 Unscheduled contacts from Sep to Dec 2021

6.9.2.1 The proportion of patients with unscheduled medical contact.

In the mixed-effect logistic regression analysis on the proportion of patients with unscheduled medical contacts from September to December 2021, the odds ratios (OR) across demographic factors such as gender, age, ethnicity, and IMD deciles were generally around 1, indicating no statistically significant differences. The confidence intervals for these ORs largely included 1, confirming that these factors did not notably affect unscheduled medical contacts for children with asthma. IMD decile 4 was an exception, showing a lower OR of 0.82 (95% CI: 0.69-0.97), suggesting a decrease in unscheduled contacts in this group. For a visual representation of the subgroup analysis, please refer to Figure 6.9, which displays the forest plot of the logistic regression.

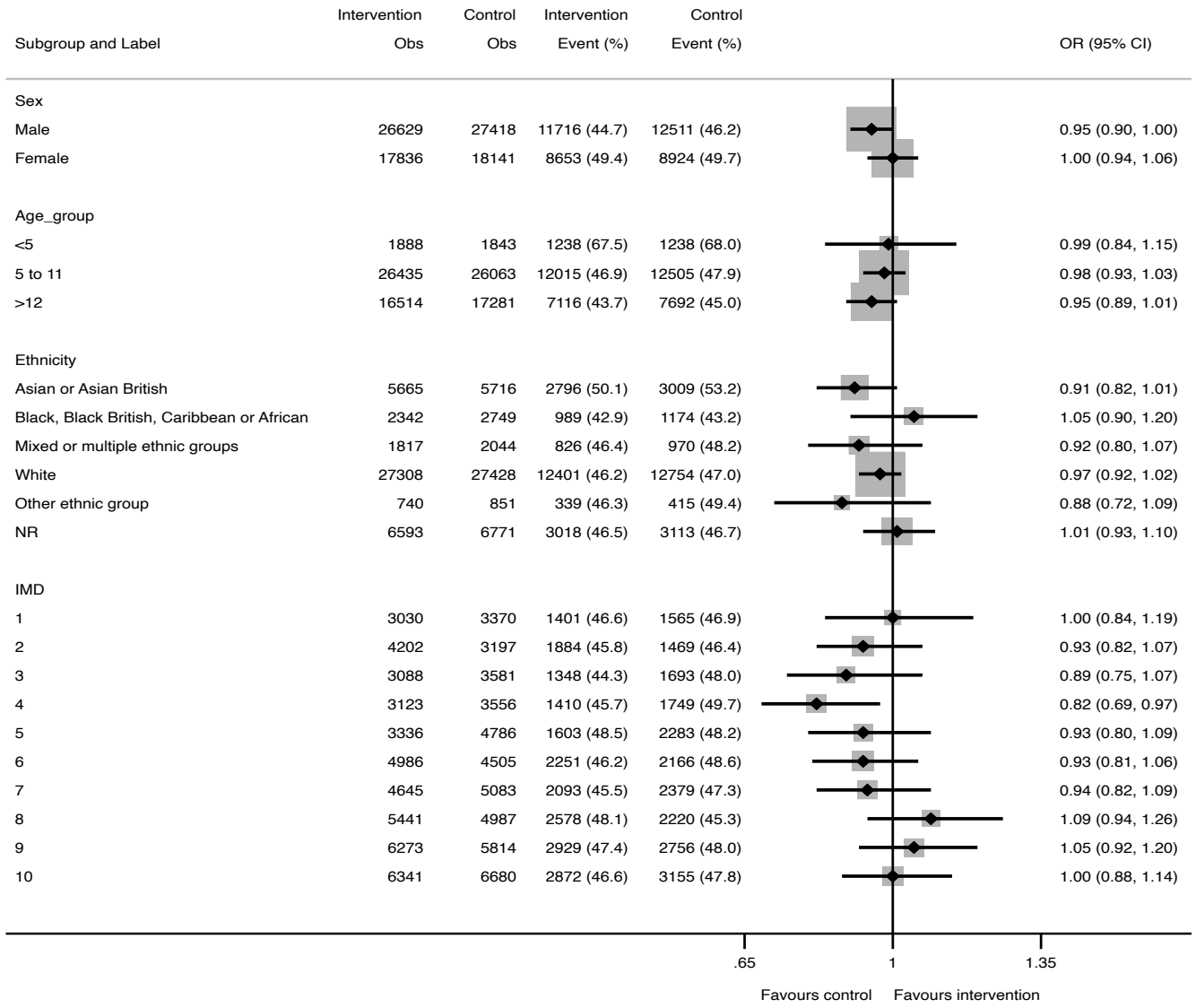


Figure 6-9 Forest plot of mixed-effect logistic regression analysis for unscheduled contacts (September-December 2021) within each subgroup analyses.

6.9.2.2 The number of unscheduled medical contact per patient.

The mixed-effect negative binomial regression for unscheduled medical contacts from September to December 2021 reveals an overall incidence rate ratio (IRR) of 1.00. The IRRs for all subgroups fell within the confidence interval, indicating no statistically significant variations in the number of unscheduled contacts across sex, age groups, ethnicities, or IMD. This suggests that these factors did not substantially influence the number of unscheduled medical contacts per patient within the studied period. For a visual representation of the subgroup analysis, please refer to Figure 6.10 (forest plot).

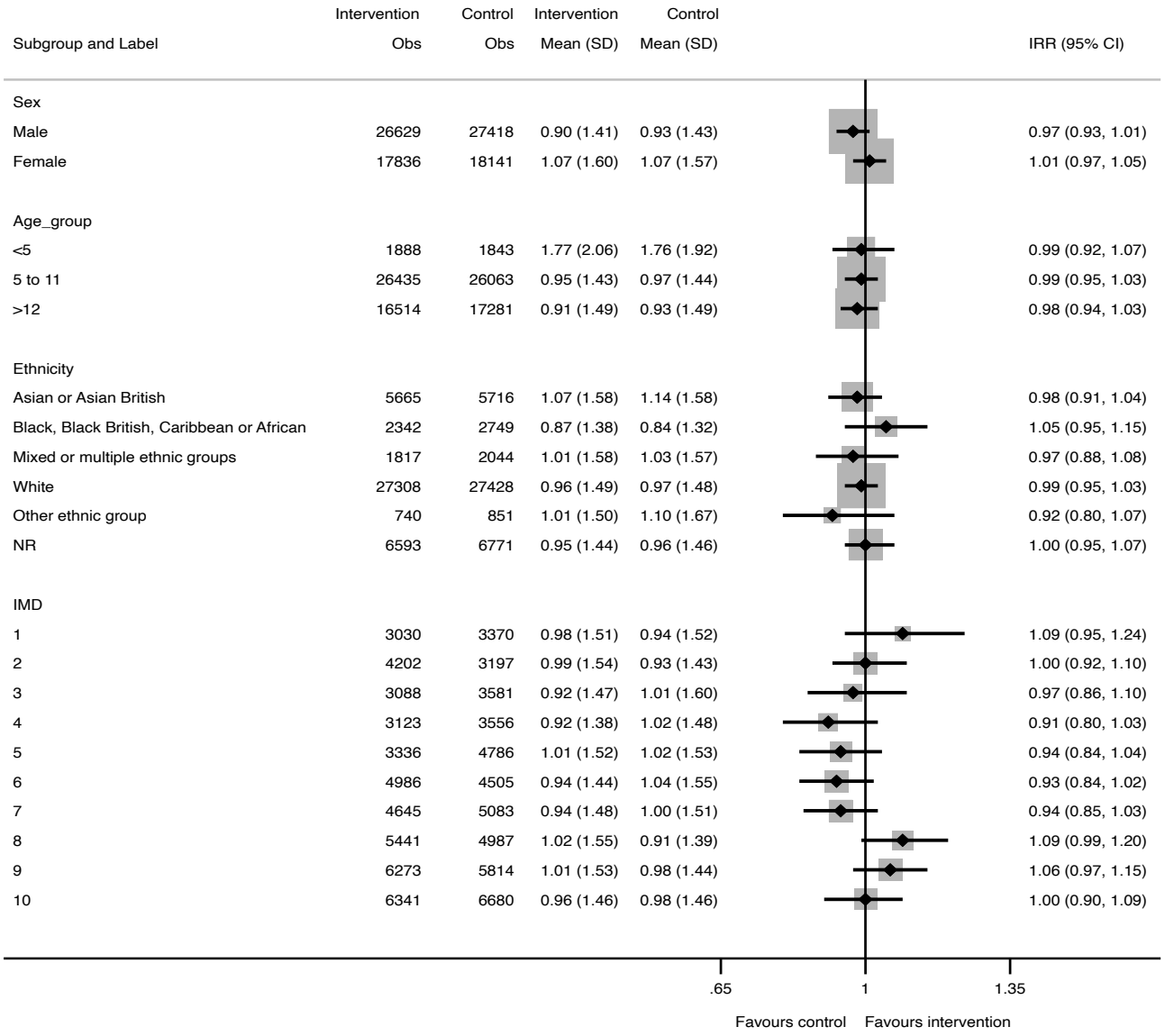


Figure 6-10 Forest plot of mixed-effect negative binomial regression analysis for the allocation estimates of unscheduled medical contact (September-December 2021) within each subgroup analyses.

6.9.3 All medical contacts from Sep to Dec 2021

6.9.3.1 The proportion of patients with a medical contact (either unscheduled or scheduled).

The subgroup analysis of the proportion of children with asthma who had any medical contact (either scheduled or unscheduled), assessed via mixed-effect logistic regression from September to December 2021, revealed no statistically significant variation across different subgroups. The odds ratios (ORs) for different groups, including gender, age categories and ethnicities, were all around 1.00, indicating no distinct difference between the groups. Similar observations were made across the IMD, with ORs mostly close to 1.00. These findings suggest that the intervention, denoted by the letter, had a consistent effect across different demographic subgroups. For a visual representation of these results, please refer to Figure 6.11, which provides a forest plot of the finding

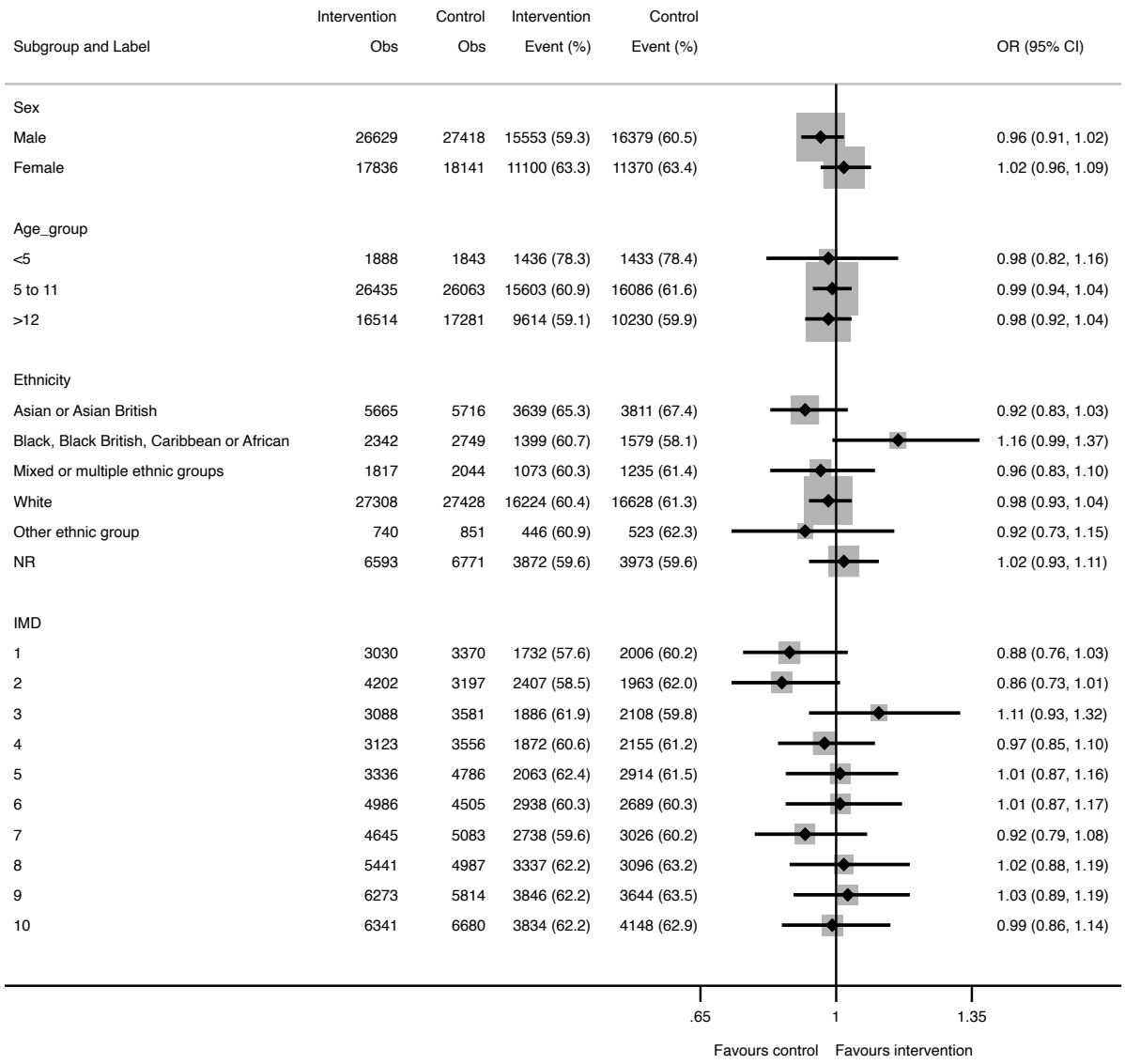


Figure 6-11 Forest plot of mixed-effect logistic regression analysis for the allocation estimates of all medical contact (September-December 2021) within each subgroup analyses.

6.9.3.2 The total number of all medical contact (either unscheduled or scheduled) per patient.

In the mixed-effect negative binomial regression for all medical contacts between September and December 2021, the IRR was approximately 1 across all subgroups. This suggests that the intervention had no statistically significant effect on the number of all medical contacts across demographic groups. The IRRs ranged from 0.93 to 1.10, showing that the intervention did not have a statistically significant influence the frequency of medical contacts differently among subgroups. To visualise these findings, please refer to Figure 6.12 (forest plot).

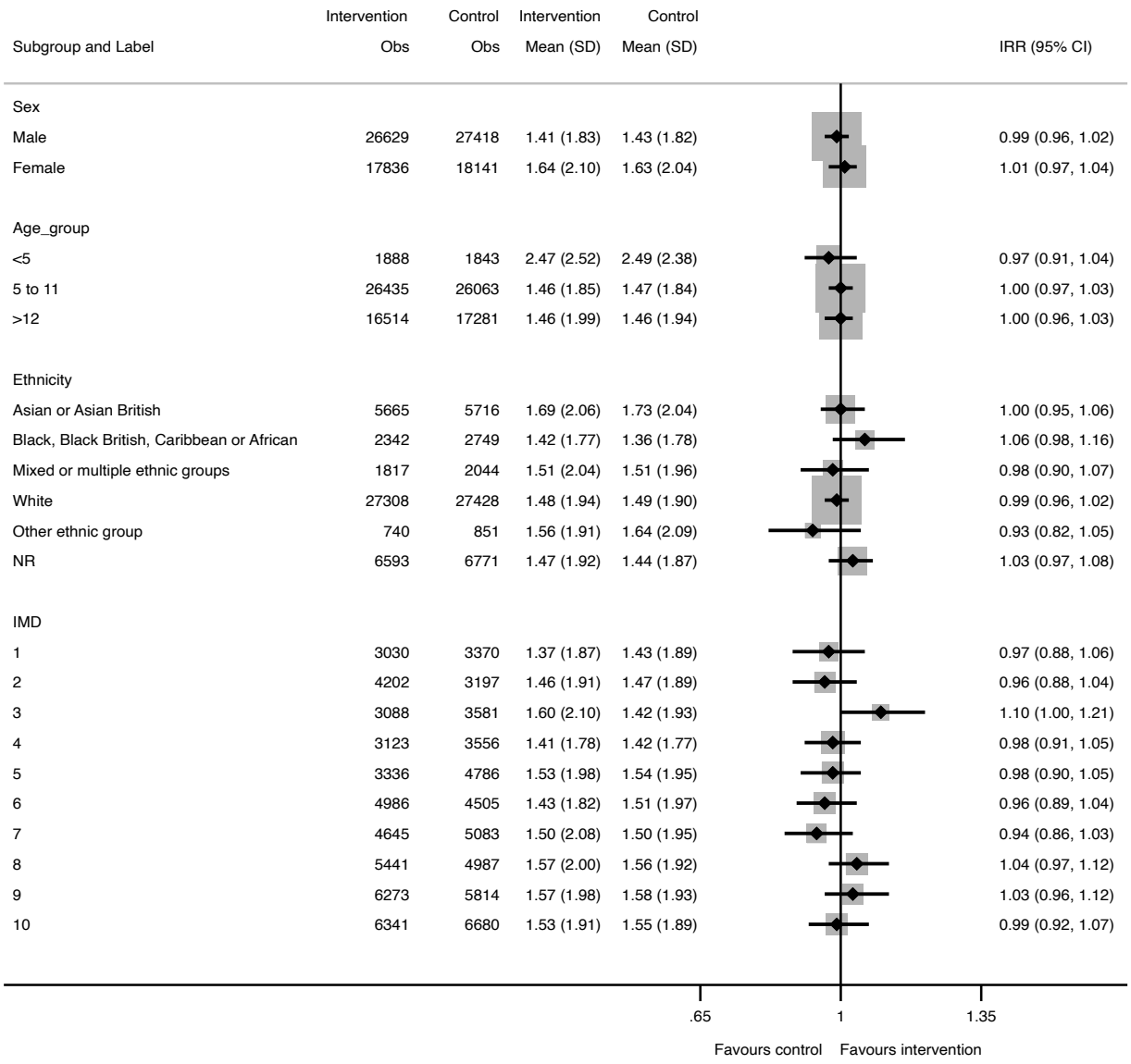


Figure 6-12 Forest plot of mixed-effect negative binomial regression analysis for the allocation estimates of all medical contacts (September-December 2021) within each subgroup analyses.

6.10 Conclusion

In conclusion, this chapter has provided a comprehensive analysis of the impact of our intervention, a letter, on prescription uptake and medical contacts (unscheduled or all contacts) in school-age children with asthma. The data analysed from various models suggest that the intervention did not notably alter the prescription uptake in August and September 2021, or during other periods.

Furthermore, the analysis of medical contacts, both scheduled and unscheduled, did not exhibit any remarkable differences between the intervention and control groups over various time frames. The consistency of these findings across different models supports the conclusion of the intervention's limited effectiveness. Key results are shown below.

		Treatment arm				*Treatment arm*			
	Time period	Intervention Events (%)	Control Events (%)	OR	95% CI	Intervention Mean (SD)	Control Mean (SD)	IRR	95% CI
(A) For all children in the intention-to-treat population									
Prescription Uptake	Aug - Sep 21	15,716 (35.3)	16,001 (35.1)	1.01	0.97 to 1.04	0.55 (0.95)	0.55 (0.93)	1.01	0.98 to 1.03
Unscheduled Contacts	Sep - Dec 21	20,369 (46.6)	21,435 (47.6)	0.97	0.92 to 1.01	0.97 (1.49)	0.98 (1.49)	0.99	0.96 to 1.02
Total Contacts	Sep– Dec 21	26,653 (60.9)	27,749 (61.6)	0.99	0.94 to 1.04	1.50 (1.95)	1.51 (1.91)	1.00	0.97 to 1.02

Table 6-16 a summary table of the key results and comparisons

Although the read receipt analysis suggested minor improvements, they were not statistically significant. Similarly, when we conducted a subgroup analysis considering variables such as gender, age bracket, ethnicity and IMD, the impact of the intervention remained not statistically significant.

So overall, the letter did not work in the way we hoped it would. In the next chapter, we will look deeper into these results, comparing them to other studies, considering the results in terms of failed study vs failed intervention, considering the impact of COVID-19 and identifying areas where we could do more research in the future.

Chapter 7: Discussion

7.1 Introduction

The previous chapters of this thesis have presented a series of analyses aimed at addressing the research objectives of this Ph.D. study. In this chapter, we will begin by restating the aim of the thesis. Subsequently, we will provide a discussion of the key findings from this Ph.D. study, drawing upon relevant existing literature. Following that, an evaluation of the study's strengths and limitations will be presented, along with reflections on their potential implications. Finally, we will outline suggestions for future research directions.

7.2 Aim of the Thesis

The PLEASANT trial showed that a simple, cost-effective intervention could increase preventer prescriptions uptake in August and reduce unscheduled medical contacts after the return to school from September to December. The direct clinical advantage of implementing these research findings in a practical setting is evident, with the potential to improve clinical outcomes and achieve significant cost savings per patient. The overall aim of the thesis was to assess the effectiveness of informing GP practices about the PLEASANT intervention in implementing this strategy in school-age children with asthma. To achieve this, the aim was divided into four specific research questions:

1. Does informing GPs about the results of PLEASANT intervention increase preventer prescription uptake in August and September 2021?

2. Will the intervention lead to a decrease in unscheduled or all medical contacts after the return to school from September to December 2021?
3. Will the confirmation of the intervention delivery show any significant findings?
4. Is there any variation in the intervention's impact based on subgroup variables, including sex, age group, ethnicity and IMD deciles?

7.3 Approach

The effectiveness of the intervention in the TRAINS study was evaluated using a pragmatic cluster-randomised controlled parallel-group trial design. The CPRD database was used to deliver the intervention and collect the necessary data. The intervention design process was carefully planned and executed, informed by behaviour change theories, aimed to evaluate the impact of a passive letter-based intervention on preventers prescriptions among children with asthma, with the goal of increasing the possibility of its effectiveness and appeal to GPs. It involved a comprehensive and multi-stage approach that lasted for six months, starting from November 2020 and concluding in April 2021.

The design incorporated feedback and insights from various sources, including GP seminars, a systematic review, the TRAINS Trial Steering Committee (TSC) and consultations with a communication specialist. These inputs helped refine the language and improve the usability of the PEMs.

The final design of the intervention, resulting from five phases of consultation and refining, encompassed several components: a two-page letter to GPs containing brief recommendations and relevant links, a detailed leaflet outlining the PLEASANT study, one-page reminder templates for assisting GPs in implementation and an email with all intervention materials. This approach was meant to give GPs a complete and informative package.

This thoughtfully designed intervention aimed to optimise engagement and increase its effectiveness. The intervention consisted of sending a letter to GPs in June 2021, both via mail and email, which informed them about the decline in prescriptions during the summer and presented the PLEASANT trial results. In addition to the letter, GPs received a supportive leaflet regarding the intervention, as well as a letter and SMS template to facilitate the implementation. The results of the implementation and its impact on prescription uptake are discussed in detail in subsequent sections.

1- **Does informing GPs about the results of PLEASANT study increase preventer prescription uptake in August and September 2021?**

This research question aimed to determine whether informing GPs about the results of the PLEASANT study could increase the uptake of preventer prescription for children with asthma during August and September 2021. This inquiry was followed through comprehensive quantitative analyses, including a mixed-effects logistic regression and mixed-effects negative binomial regression, accounting for gender, age group, ethnicity and baseline data from 2019 and 2020. Detailed results of this analysis are available in Chapter 6.

The findings revealed no statistically significant difference in the proportion of children collecting a prescription or the incidence rate of prescription uptake between the intervention and control groups. Therefore, the data suggest that the intervention did not statistically significantly increase the uptake of preventer prescriptions during the specified period.

2- Will the intervention lead to a decrease in unscheduled or all medical contacts after the return to school from September to December 2021?

The research question explored whether the intervention would reduce unscheduled or all medical contacts after children with asthma returned to school from September to December 2021. The outcomes included: the proportion of patients with unscheduled medical contacts; the number of unscheduled medical contacts per patient; the proportion of patients with any medical contacts and the total number of medical contacts per patient over various periods.

Throughout the analyses, the intervention did not demonstrate statistically significant effects in any of the models. Specifically, the odds ratios and incidence rate ratios for the months of September, October, November, December, as well as the entire period from September to December 2021 were consistently 1.00. This result indicates no statistically significant difference between the intervention and control groups, suggesting that the intervention did not reduce unscheduled or all medical contacts for children with asthma upon their return to school in the specified period.

3- **Will the confirmation of the intervention delivery show any significant findings?**

The research focused on whether the read receipt confirmation for the intervention delivery would yield significant findings. A total of 694 practices using the CPRD were contacted through postal mail and email. As part of our engagement tracking strategy, we utilised the email read receipt feature provided by CPRD, which confirmed whether our email was opened by the contact lead at each practice.

Following the intervention period, we received read receipts from 302 (45.5%) of the practices contacted. This data was vital in analysing the practices that opened our email compared to the control group. For more detailed information on this engagement tracking process, please refer to Section 6.8.1.

Subsequent analyses evaluated the intervention's impact on a range of outcomes within this subgroup. The odds ratios and incidence rate ratios indicate that there were no statistically significant differences in any outcomes between the groups that confirmed receipt of the intervention and the control groups.

It is noteworthy, however, that there were slight increases in some of the odds ratios and incidence rate ratios (ranging from 1.02 to 1.04). Although these changes were not statistically significant, they suggest a possible trend towards slightly higher rates of prescription uptakes.

Overall, no statistically significant findings were shown in the analysis considering the impact of the intervention with read receipt confirmation on a range of outcomes related to prescription uptakes and medical contacts among children with asthma.

4- **Is there any variation in the intervention's impact based on subgroup variables, including sex, age group, ethnicity and IMD deciles?**

The study conducted a subgroup analysis to assess whether the intervention's impact varied based on variables such as sex, age group, and ethnicity.

Regarding prescription uptake in August and September 2021, logistic regression and negative binomial regression analyses showed odds ratios and incidence rate ratios close to 1 with 95% confidence intervals including 1 across all the subgroups. This suggests no statistically significant differences in the prescription uptake rates based on these factors.

Similarly, for unscheduled contacts and all medical contacts from September to December 2021 analyses did not reveal any statistically significant differences in odds ratios or incidence rate ratios across different demographic factors.

In conclusion, the intervention's impact does not seem to vary based on the demographic subgroup variables studied, including sex, age group, and ethnicity. These factors did not statistically significantly affect the uptake of asthma preventer prescriptions, unscheduled medical contacts, or any medical contacts within the study period.

7.4 Key findings and comparison with existing literature

Despite the theoretical underpinnings from models such as the Health Belief Model (HBM) and the Theory of Planned Behaviour (TPB), the intervention did not achieve the intended outcomes.

We predicated our approach on the HBM, expecting that GPs' recognition of the critical nature of asthma management and the advantages of modifying their prescribing habits would incite behavioural changes. These assumptions may have held true if the intervention effectively reached the GPs; however, it might have been obstructed at the practice manager level or by whoever initially received it. If we were to redesign the intervention, it may be necessary to ensure that it is engaging enough to capture the attention and interest of the first contact point, thereby facilitating its passage to the GPs. Likewise, according to the TPB we believed that the attitudes of GPs, along with subjective norms and their perceived ability to enact change, would significantly influence their reaction to our intervention. Nonetheless, our findings suggest that these

theoretical models did not anticipate the complexities involved in altering behaviours within this particular real-world setting.

In terms of measuring engagement with the intervention, specifically through the use of email read receipts, we observed that over 45% of practices accessed the emails. Despite this, there was no noticeable impact on their practices. Although there were minor increases in some odds ratios and incidence rate ratios, suggesting a possible inclination towards increased prescription rates. These variations were not statistically significant, highlighting the difficulties in quantifying and interpreting the intervention's 'dose received.'

This lack of significant outcomes prompts a reassessment of how these behaviour change theories are applied in practical scenarios. A critical oversight in our analysis was the consideration of intervention fidelity, which encompasses the precision of implementation according to the planned intervention (the 'dose delivered') and the engagement level with the intervention content (the 'dose received').

Given that each practice was provided with both letters and at least one email, relying solely on email read receipts to gauge the 'dose received' is insufficient. This method does not account for whether the practices actually internalised or acted upon the information provided. The assumption that practices did not access or engage with the intervention content based solely on email interaction overlooks the multifaceted nature of communication and engagement. It overlooks other potential avenues through which the intervention's message could have been received and considered within the practices.

This critique underscores the necessity for a more details understanding and discussion of intervention fidelity within our study. It highlights the importance of thoroughly examining both the 'dose delivered' and the 'dose received' to gain a comprehensive view of an intervention's implementation and its potential effects on targeted behaviours. This reflection is crucial for advancing our comprehension of how to effectively design and assess interventions within healthcare settings.

This finding aligns with the systematic review findings (Chapter 3), which showed that printed educational materials exert limited influence on GP prescribing patterns. For instance in asthma prescribing, Søndergaard et al. (2002) found that postal feedback, even when comprising detailed clinical data on asthma drug prescriptions and associated guidelines, had no significant effect on GP prescribing patterns (Søndergaard *et al.*, 2002).

It should be noted though the studies in the systematic review have not investigated the impact of PEM on the prescription of asthma preventer medications in school-age children. Alongside this, many of these studies were a lot smaller and so would have been less able to show evidence for small effects unlike TRAINS which had a large sample size. Also, only one (Guthrie et al. 2016) used email. Furthermore, the majority of these studies opted for active controls, with PEMs often serving as a control group instead of the main intervention under study. Also, only one of the studies employed a two-arm structure to directly compare PEMs with a usual care control group like TRAINS.

Even though the intervention did not work, the study also uncovered a recurring annual decline in prescription uptake during August persisted throughout the study. Additionally, the expected peak in unscheduled care visits from September for school-aged children with asthma was also consistently observed, as shown in the time series plots (Chapter 6). The decrease in August prescriptions aligns with the PLEASANT trial and Sears and Johnston's 2007 study (Sears and Johnston, 2007; Julious *et al.*, 2011, 2018), while the exacerbation peak from September echoes existing literature documenting this pattern among school-aged children (Gergen, Mitchell and Lynn, 2002; Kimes *et al.*, 2004; Johnston *et al.*, 2005; Julious *et al.*, 2011, 2018). This seasonal pattern is often attributed to factors such as increased exposure to respiratory viruses and allergens and shifts in medication adherence upon school resumption (Murray *et al.*, 2006).

The COVID-19 pandemic added an unexpected layer to the data, revealing a significant surge in the prescriptions of asthma preventers in March 2020, in contrast to the preceding month, February 2020 (Refer to Section 6.7.1). This observable peak corroborates findings reported in other studies (C. I. Bloom *et al.*, 2021; Dhruve *et al.*, 2022). Concurrently, the data showed a significant decline in medical contacts, including both all and unscheduled contacts, during the lockdown compared to the previous year (Refer to Section 6.7.2). This trend is also consistent with results found in additional studies (Boer *et al.*, 2021; Shah *et al.*, 2021; Shah, Quint and Sheikh, 2022).

Assessing the success of the PLEASANT trial requires a detailed analysis of its various outcomes and objectives. Initially, the trial aimed to address the seasonal decrease in asthma prescriptions during summer, a period typically marked by lower medication adherence. This was achieved through a direct intervention where GPs sent letters to the parents of asthmatic children, emphasising the importance of continuous medication use over the summer holidays.

Despite not meeting its primary objective of reducing unscheduled medical contacts in September, the trial observed a notable increase in asthma prescription uptake not only in August but also in September. However, the primary outcome's time window might not have optimally captured the seasonal peak in unscheduled medical contacts, which begins in September and extends through autumn to December. This misalignment

suggests that while the trial didn't meet its primary objective, it demonstrated a potential long-term beneficial impact on healthcare utilisation, evidenced by the reduction in total medical contacts over the following year. The increase in prescription uptake during both August and September indicates a degree of success in influencing behaviour during a critical period for medication adherence.

Moreover, the trial's health economic analysis added another dimension to its success. It revealed that the reduction in total medical contacts over a year resulted in a significant cost-saving of £36.07 per patient annually. This economic benefit, coupled with the low cost of implementing the intervention (£1.34 per child), demonstrated the cost-effectiveness of the intervention. With a 96.3% probability of cost-saving, these findings underscore the potential of simple, cost-effective interventions to make substantial contributions to public health and healthcare expenditure.

Thus, while the PLEASANT trial did not achieve its primary endpoint, its impact on prescription uptake, long-term healthcare utilisation, and cost-effectiveness highlights partial success. It effectively increased medication adherence during a typically low adherence period and led to economic benefits, though it did not significantly impact the primary endpoint of reducing unscheduled care in September. These outcomes highlight the complexities of influencing healthcare behaviours and point towards areas for future research and development of interventions.

The TRAINS study used a pragmatic cluster-randomised controlled trial design, which is robust for evaluating real-world interventions. However, unlike the PLEASANT trial which involved direct delivery of letters to families by GPs, the TRAINS study only suggested that practices deliver letters. This approach changes the nature of the intervention from a direct to an indirect method of communication. The effectiveness of such an indirect approach can be questioned since it relies heavily on the willingness and capacity of the practices to further disseminate the intervention materials.

While the intervention was designed with input from behaviour change theories, there might have been a gap in applying these theories effectively to influence GP behaviours. Theories like the Health Belief Model and the Theory of Planned Behaviour emphasise the importance of perceived severity, benefits, and behavioural control. The indirect nature of the intervention might not have sufficiently addressed these aspects to motivate change in GP behaviour. However, the potential effectiveness of these theoretical frameworks might have been realised if the GPs had actually received the intervention letter. Without clear evidence of who exactly received it, it's impossible to definitively say whether the lack of impact was due to the intervention's design or its failure to reach the intended recipients.

Assessing implementation differs from conducting an implementation study. The former evaluates the impact of a recommendation, as seen in the TRAINS study, where practices

were advised to send reminder letters. In contrast, implementation studies directly apply and monitor interventions, ensuring strategies are executed as intended. The TRAINS approach, focusing on recommendations, differs from traditional implementation studies, which involve direct intervention delivery and oversight.

The TRAINS study involved multiple stages of consultation for refining the intervention, which is a strength. However, the engagement of GPs with the intervention and their compliance in further communicating to families is unclear. Without a mechanism to track this engagement or the actual delivery of letters to families, it's challenging to determine the true reach and impact of the intervention.

While the study was successful in terms of its design and execution, particularly in using a large dataset for analysis, the nature of the intervention raises questions about its direct impact. The study's success, therefore, may be more aligned with its ability to provide insights into intervention strategies rather than the effectiveness of the intervention itself.

In assessing the TRAINS results, the question of whether it is the study or the intervention that has failed is best answered by identifying the intervention as the unsuccessful element. The study, built on routine data, had a large sample size, able to show small effects precisely. It accurately captured the anticipated August decline and September peak. In this context the study was a successful study.

Therefore, though the study in itself was successful the intervention failed to have an effect and so the intervention failed. The intervention's lack of effect could be attributed to multiple stages of its execution, as illustrated in Figure (7-1).

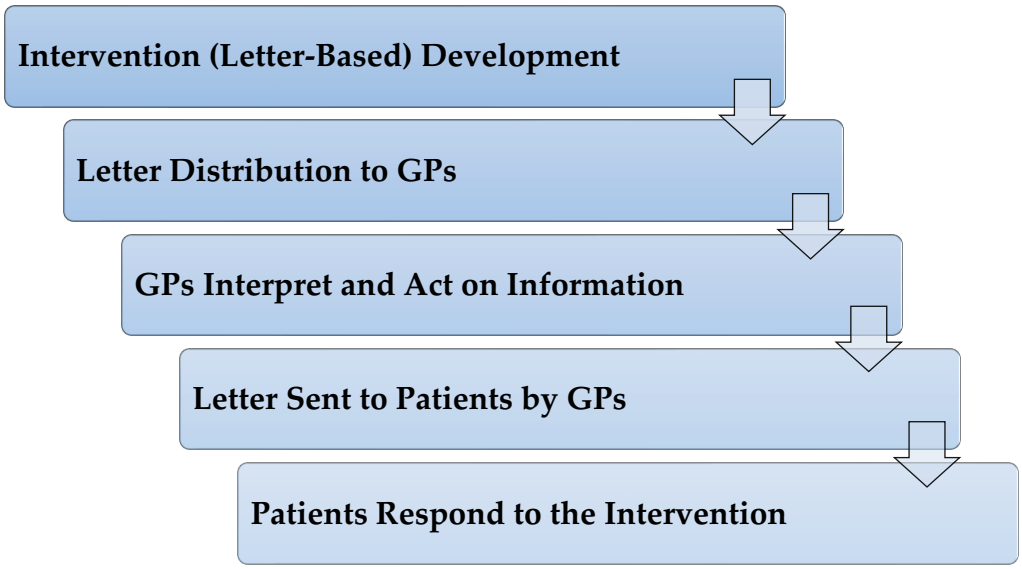


Figure 7-1 Factors Influencing the Intervention's Effectiveness

1. Intervention Development: Our intervention, a letter, might not have been the most impactful method. As discussed earlier, the overall effectiveness of printed educational materials in instigating change is questionable, possibly leading to the observed lack of impact on prescription uptake and unscheduled hospital visits.

2. Letter Distribution to GPs: The intervention hinged on the assumption that the letters would reach the intended GPs, and that these GPs would read and agree with the importance of the contents. Any failure or delay in the distribution process could have adversely affected the intervention's effectiveness.

3. GPs Interpret and Act on Information: Once the GPs received the letters, their ability and willingness to act on the information provided became crucial. Limited resources, competing priorities, and insufficient support from other healthcare professionals might have hampered the GPs' ability to implement the recommended changes (Zwolsman *et al.*, 2012; Sadeghi-Bazargani, Tabrizi and Azami-Aghdash, 2014).

4. Letter Sent to Patients by GPs: Assuming the GPs acted upon the received letter, the intervention's success further depended on this information's distribution to patients. Factors such as the clarity of the information relayed, the medium of communication, and timing could have significantly influenced patient response. Also, the text reminder may not have been as effective since it was not tested in the PLEASANT study that used a letter reminder.

5. Patients Respond to the Intervention: Even after receiving the letter, patient response would be influenced by various factors. For instance, parents might have prioritised other concerns, like planning holidays, over picking up a prescription. The efficacy of the intervention is therefore highly dependent on the complex and multifaceted nature of patient behaviour.

In the TRAINS study, the shift to sending two intervention letters simultaneously in June, rather than at different times due to the COVID-19 pandemic, raises critical questions about intervention dosage. It's important to acknowledge that this adjustment was

prompted by delays in obtaining ISAC ethics approval, attributable to reduced operations during the COVID-19 pandemic, which necessitated this change. This change prompts a revaluation of whether a 'bigger dose' in terms of communication frequency can truly enhance intervention effectiveness. Contrary to the assumption that more frequent communications would lead to better outcomes, findings from similar studies suggest that the success of interventions often relies more on their quality and relevance (Grimshaw *et al.*, 2012). This insight implies that well-crafted, timely messages tailored to GPs' contexts may have a greater impact than multiple, less focused communications.

Additionally, after sending out the intervention, we received some responses from practices, indicating that they were looking for incentives to facilitate the implementation of the recommended changes. These responses highlight the importance of considering potential barriers and motivations that influence healthcare providers' willingness to adopt new practices.

External factors beyond the control of the study may also have affected the intervention's effectiveness. The unprecedented COVID-19 pandemic, causing distractions and competing priorities, may have also impacted outcomes, which we will discuss in detail later (Tuttle, 2020, p. 19).

In conclusion, the letter-based intervention failed to improve prescription uptake or reduce unscheduled medical contacts. This emphasises the need for further investigation

and alternative strategies to optimise asthma management in school-aged children. Similarly, more effective methods for disseminating research findings to GPs warrant further exploration.

Had the intervention achieved its intended outcomes, the next step would be to recommend all publicly funded trials primary care trials to disseminating their published findings to GP practices through a simple mailing. Currently, the dissemination strategy primarily relies on GPs' proactiveness in reading academic journals to access new research findings. This approach may limit the reach and impact of potentially practice-changing insights which has its limitations but the evidence from this study is that a mailing does not complement this.

7.5 Estimands Framework in the TRAINS Trial

The application of the estimands framework in the TRAINS trial is a critical aspect for understanding and interpreting the outcomes of this cluster-randomized trial. This framework, central to the trial's analysis, profoundly influences the interpretation of its results and the conclusions drawn.

7.5.1 Participant-Average Treatment Effect as a Focus

The TRAINS study's adoption of the 'participant-average treatment effect' as its primary estimand was a strategic decision, aligning with the methodological guidelines of ICH E9 (ICH, 1998). This choice placed emphasis on assessing the impact of the intervention at the individual level, particularly on each child's prescription uptake. Such a focus is crucial in understanding how the dissemination of information about the PLEASANT trial results affected individual health behaviours, specifically among children with asthma.

7.5.2 Analysis and Interpretation of Findings

Despite the methodological soundness of this approach, the findings from the TRAINS trial as discussed before revealed no significant changes in prescription behaviour or reductions in medical contacts following the intervention. The consistent odds ratios and incidence rate ratios, remaining close to 1.00 across both intervention and control groups,

pointed to a minimal impact of the intervention. This consistency in the results across different demographics underscores the limited efficacy of the intervention in altering healthcare behaviours at the individual level.

7.5.3 Reflecting on the Estimands Framework Implications

The choice of estimand in the TRAINS trial has profound implications for the design and evaluation of healthcare interventions. While the participant-average treatment effect provided a clear focus on individual outcomes, the lack of significant findings raises questions about the effectiveness of using a letter to disseminate information in influencing GP behaviours and healthcare practices. The results suggest a need for a more comprehensive approach in future interventions, considering both individual behaviours and broader systemic factors within healthcare settings.

7.5.4 Moving Forward: Implications for Future Research

The application of the estimands framework in the TRAINS trial offers valuable lessons for future research. It emphasises the importance of carefully selecting the target estimand to align with the research objectives and the practical realities of healthcare intervention. Future studies might benefit from exploring a blend of individual and systemic focus, ensuring that interventions are not only theoretically sound but also practically effective in real-world settings.

7.6 Strengths and limitations of the study

7.6.1 Strengths

7.6.1.1 Utilisation of CPRD for intervention and data collection

The advantage of the study design is that it used CPRD to both send the intervention and collect the data. The GP practices were unaware of their participation in the study, thus eliminating the potential for biases related to recruitment and data collection. So, it made the study pragmatic and relevant to the real world. Moreover, CPRD offered a cost-effective and efficient approach, eliminating the need for additional resources for data collection, thereby making the study more economical. It also facilitated access to a large and diverse patient population, enhancing the generalisability of the findings (CPRD, 2022). Furthermore, CPRD enabled continuous, real-time data collection, ensuring data integrity and reducing the likelihood of missing or incomplete data. Lastly, the use of CPRD allowed for the monitoring of the intervention over time, providing valuable insights into the intervention's long-term impacts and effectiveness.

7.6.1.2 Large sample size and generalisable data

The study benefitted from a large sample size, as CPRD covers approximately 20% of the UK's population (CPRD, 2022). A total of 1,326 GP practices in England, including 90,583 individuals were included in the study. This allowed for generalisable data and the

ability to perform several relevant subgroup analyses. As far as I am aware this is the largest sample size, in terms of number of clusters, that has ever been conducted in the UK.

Furthermore, stratification by practice size could be considered as an additional strength. This approach ensures that participants are evenly distributed across different levels of deprivation, enhancing the study's ability to account for socioeconomic factors that may impact asthma management and outcomes. Stratification by practice size deciles adds robustness to the study's findings and strengthens the validity of its conclusions.

7.6.1.3 Cluster-randomised controlled trial design

Another strength of the study is using a cluster-randomised controlled trial design, which reduces the risk of contamination between intervention and control groups (Torgerson, 2001; Hayes and Moulton, 2017). By randomising at the level of GP practices, the study minimised the possibility that the intervention could inadvertently influence the control group, maintaining the integrity of the comparison between the two groups. This design also allowed for a more accurate assessment of the intervention's effectiveness in real-world settings, as it accounted for potential variations in GP practices' approaches to asthma management and patient care.

7.6.2 Limitations

7.6.2.1 Impact of COVID-19

The COVID-19 pandemic has had far-reaching effects on various aspects of healthcare, including the design and implementation of interventions (Onyeaka *et al.*, 2021). In this section, we discuss the impact of the COVID-19 pandemic on the intervention's design, engagement with GPs and the necessity to add an extra baseline to account for the non-standard year of 2020.

Impact on intervention design

The COVID-19 pandemic presented unique challenges in designing the intervention (Chapter 4). Ideally, our approach would have included more seminars to meet more primary care doctors, nurses and practice managers to enhance and improve the intervention and to have done it face to face. This was not possible due to the various lockdowns to contain the pandemic, which unfortunately did not let me advance the intervention as we originally planned and Envisioned (Alyami *et al.*, 2022). In addition, the rapidly changing healthcare landscape necessitated adaptability, which might have limited the intervention's effectiveness. The focus of GPs and other healthcare professionals shifted toward managing the pandemic's impact and addressing their patients' urgent needs (Harper *et al.*, 2020).

Engagement with general practitioners

During the pandemic, GPs faced huge pressure, as they had to adapt to new protocols, increased patient demands and the challenges of delivering healthcare remotely (Onyeaka *et al.*, 2021). Additionally, the pandemic likely impacted GPs' engagement with the intervention, as they may have had limited time and resources to focus on the materials provided and implement the necessary changes in their practice (Rubinelli *et al.*, 2020).

Extra baseline year

As 2020 was not a standard year due to the COVID-19 pandemic, it was necessary to add an extra baseline to account for the unique circumstances that may have affected the outcomes of the study. As a result, we decided to include 2019. By adding this additional baseline, we aimed to ensure that the results more accurately reflected the intervention's effectiveness.

Timing of the intervention

The intervention was originally planned to be sent out in two separate intervals, approximately a week or two apart. However, due to the impact of the COVID-19 pandemic and the delay in obtaining ISAC approval due to COVID research being prioritised, we were only able to send out the interventions simultaneously in June 2021.

Notably, during this time, the rollout of the COVID-19 vaccination campaign (NHS, 2021) was underway, which likely posed significant challenges for GPs. Their focus was understandably diverted to administering vaccines and addressing patient concerns related to vaccination. This concurrent demand on GPs' time and attention could have influenced the intervention's effectiveness, as it may have affected their capacity to fully engage with and implement the recommendations provided in the intervention letter.

In conclusion, the COVID-19 pandemic had a potential impact on various aspects of the study. It affected the study's design, made it more challenging to engage with GPs and required the inclusion of an additional baseline year to account for the unique circumstances of 2020. It is possible that under normal circumstances, with more opportunities for engagement and collaboration with GPs, the intervention could have been more effective. The pandemic-related disruptions to healthcare delivery may have affected the study's results, making it difficult to draw definitive conclusions about the intervention's effectiveness in a non-pandemic context. Overall, the impact of COVID-19 on this study highlights the importance of understanding and accounting for external factors that can influence the outcomes of healthcare interventions and research.

7.6.2.2 Routinely collected data from CPRD

This study used routinely collected data from CPRD, which comes with certain limitations, such as missing data and inconsistencies in definitions. While primary outcomes of prescription update would be less impacted by these concerns secondary outcomes may be more susceptible to these issues. The data relies on healthcare providers inputting information as part of their routine patient care and information not coded in the patient record will not be available (CPRD, 2022). Furthermore, CPRD does not provide standardised definitions for diagnoses, treatments and health information, potentially leading to inconsistent results between studies using the same data. Researchers should consider these limitations when planning their research and interpreting the results.

7.6.2.3 Potential inaccuracies in coding medical contacts

The coding methodology for unscheduled medical contacts could have affected one of the outcomes. We adopted the PLEASANT study's coding methods, which might have introduced potential biases. To generate reliable results and mitigate the effect of potential biases, it is essential to ensure the coding methods' precision and consistency in such studies.

7.6.2.4 Exploratory Subgroup Analyses Limitation

Our exploratory subgroup analyses aimed to uncover how different demographic groups responded to the intervention. However, by focusing on confidence intervals without adjusting for multiple comparisons, we prioritised trend exploration over statistical significance. This approach, while valuable for generating hypotheses, necessitates cautious interpretation. The absence of p-value adjustments means our findings offer preliminary insights rather than definitive conclusions, representing a limitation in our ability to generalise the heterogeneity of treatment effects. This methodological choice underscores the exploratory nature of these analyses and highlights the need for further research to validate our observations.

7.6.2.5 Lack of intervention assessment

Another limitation of the study is that we have no plans to contact the practices to assess if the intervention was sent. This is because this is a real-world implementation study. This lack of direct feedback from the practices could impact the interpretation of the results, as it is unclear whether the intervention was properly implemented or not. This makes it challenging to draw definitive conclusions about the intervention's effectiveness and could potentially mask any actual effect of the intervention on prescription uptake and unscheduled hospital contacts.

7.7 Implications for GPs and Future Research Directions

7.7.1 Implications for GPs

The recurring spike in unscheduled patient contacts after returning to school in September underscores a predictable challenge that demands proactive action. For GPs, the implications are clear: adopting innovative communication and intervention strategies is essential to enhance patient care, especially in managing conditions like asthma. GPs should consider the following:

- **Implementing Diverse Communication Strategies:** Exploring and utilising various mediums, such as phone consultations or educational workshops, can aid in the effective dissemination of research findings and recommendations. This approach can support GPs in integrating new insights into their practice, improving patient outcomes.

- **Adapting to Advanced Implementation Levels:** Shifting focus from individual practices to broader systems, such as Integrated Care Systems (ICS), may offer a strategic advantage. By leveraging ICS infrastructure, GPs can facilitate the widespread distribution of preventative measures, such as reminder systems, enhancing efficiency and reach (Charles *et al.*, 2018).

- **Exploring Comprehensive Care Models:** Embracing collaborative care strategies that involve a team of healthcare professionals can significantly improve the management of chronic conditions. This model promotes a more integrated and consistent approach to patient education and care.

7.7.2 Future Research Directions for Grant Proposals

Building on the findings from the current study, the following research areas could form the basis of a grant proposal aimed at enhancing GP practices and patient care:

- **Investigating Actual Medication Adherence Patterns in Children:** Before advancing with interventions aimed at improving medication uptakes, it's crucial to examine whether children really do stop taking their asthma medication during summer or if the observed reduction in medication collection is due to other factors such as being on holiday. This investigation will help determine if there is an adherence issue or if current assumptions need to be revisited. The outcomes of studies like Trains and PLEASANT, which did not achieve their expected results, suggest the importance of understanding the real adherence patterns as a foundational step.

- **Evaluating Alternative Communication and Intervention Techniques:** Research should focus on assessing the effectiveness of different communication channels and intervention methods in improving the implementation of recommendations by GPs. This includes examining the role of technology, such as SMS reminders, and other direct communication methods.

- **Developing and Testing Comprehensive Toolkits for GPs:** Propose the creation of a toolkit that includes resources for identifying at-risk patients, guidelines for prescription reminders, and materials for effective communication with families. This project would aim to provide GPs with a practical resource to improve care delivery (Thoele *et al.*, 2020).

- **Assessing the Impact of COVID-19 on Healthcare Delivery:** Given the ongoing challenges posed by the COVID-19 pandemic, research should explore its effects on GP practices and patient care. This includes adapting study designs and interventions to address the changing healthcare landscape.

- **Conducting Qualitative and Mixed-Methods Research:** Investigate the real-world implementation of interventions within GP practices. This research would seek to uncover the factors influencing the success of interventions and gather insights to inform future projects.

For GPs, the message is to remain adaptable and proactive in integrating research findings into their practice, exploring new communication methods, and participating in collaborative care models. Future research should aim to build on these insights, focusing on practical interventions, the impact of current global health challenges, and the effectiveness of different communication strategies. This approach will not only enhance the quality of patient care but also contribute to the body of knowledge on effective healthcare delivery strategies.

7.8 Overall summary

To the best of our knowledge, this is the largest cRCT study, in terms of number of clusters, that has been undertaken in the UK. The importance of its subject matter cannot be overstated, as it addresses one of the most prevalent chronic long-term conditions in the world, and especially in children. This importance is highlighted by the annual August drop in prescription uptake and the "September peak" in school-aged children with asthma. The PLEASANT trial addressed these issues through a simple postal intervention that showed promising results in improving asthma outcomes for children and GPs.

The intervention was designed to inform general practitioners about the PLEASANT trial results and encourage them to send reminder letters to parents of children with asthma,

which demanded fairly minimal effort from the GPs. It fits within the common use of PEMs as knowledge translation tools.

Despite the potential benefits and cost-saving implications of such an intervention, the intervention did not achieve the desired outcomes. There were no statistically significant differences found in either the primary and secondary outcomes, including prescription uptake, unscheduled medical contacts and total medical contacts.

The consistency of our trial data with previous work instils confidence in these findings, particularly as the observed trend of a decrease in prescription uptake during the summer holiday and the expected September peak in unscheduled care visits for school-aged children with asthma persisted. This is indicating an ongoing unresolved issue.

With the understanding that our findings may have been influenced by the COVID pandemic, it appears that passively informing GP practices of research findings may not be an effective knowledge translation strategy. This insight has important implications for the future dissemination of other PEMs, such as toolkits.

In conclusion, although the study was successful in terms of its design and implementation, the intervention itself failed to yield significant impacts. The results underscore the need for further research and more effective strategies to improve asthma management in school-age children, particularly around their return to school.

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Appendix

Appendix A: Search strategy

Embase <1974 to 2023 Week 18>
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to May 10, 2023>

1	Family Practice/	148694
2	(family adj practice$).mp.	81969
3	(community adj practice$).mp.	6214
4	(institution$ adj practice$).mp.	4179
5	(private adj practice$).mp.	42152
6	General Practitioners/	122095
7	Occupational Health Physicians/	2133
8	Physicians, Primary Care/	121716
9	(family adj (doctor? or physician? or practitioner?)).mp.	53060
10	Group Practice/	16087
11	Physicians, Family/ [Primary Care]	128797
12	(general adj practice$).mp.	162643
13	(family adj medicine).mp.	35590
14	(group adj practice$).mp.	22968
15	(physician$ adj practice$).mp.	11194
16	(solo adj practice$).mp.	1309
17	Hospitalists/	44157
18	Osteopathic Physicians/	956
19	(community adj (doctor? or physician? or practitioner?)).mp.	3212
20	(general adj (doctor? or physician? or practitioner?)).mp.	211520
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	549236
22	Audiovisual Aids/	7868
23	Posters as Topic/	190084
24	Textbooks as Topic/	35682
25	Periodicals as Topic/	221439
26	print$.tw.	151654
27	book?.tw.	70560
28	pamphlet?.mp.	9208
29	guideline$.mp.	1573730

30	(postcard$ or post-card$).mp.	17614
31	textbook$.mp.	27252
32	(hard adj cop$).tw.	3104
33	((static or enduring or educat$ or teach$ or learn$ or instruction$ or train$) adj2 material?).tw.	36601
34	bulletin?.tw.	9296
35	message$.tw.	165336
36	((static or enduring or educat$ or teach$ or learn$ or instruction$ or train$) adj2 document?).tw.	1792
37	poster?.tw.	42539
38	manual$.tw.	377389
39	serial$.tw.	356210
40	publication$.mp.	646192
41	journal$.tw.	476891
42	monograph?.mp.	12672
43	paper$.tw.	2216943
44	Books/	40621
45	Medical Illustration/	9502
46	exp Manuals as Topic/	40511
47	Exhibits as Topic/	191377
48	Teaching Materials/ [Educational Materials]	107762
49	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48	5798671
50	(online or on-line).tw. [Delivery Method]	556406
51	((web adj page$) or webpage$).tw.	8383
52	(web-site$ or website$).tw.	114045
53	(handheld adj2 computer$).tw.	1071
54	Telefacsimile/	1001
55	Electronic Mail/	33325
56	exp Computers/	249435
57	exp Internet/	225648
58	exp Computer-Assisted Instruction/	119555
59	exp Online Systems/	47535
60	cyber$.tw.	23564
61	electronic bulletin board$.tw.	122
62	(e-bulletin adj board$).tw.	0
63	www.tw.	5578
64	world wide web$.tw.	6925
65	webbased$.tw.	1255
66	(web adj based$).tw.	100838

67	virtual.tw.	208868
68	(pocket adj PC$).tw.	111
69	personal digital assistant$.tw.	2245
70	Internet$.tw.	162144
71	email$.tw.	43112
72	(list adj serv$).tw.	757
73	(compact adj disc).tw.	665
74	CD-ROM.tw.	2557
75	(flash adj drive?).tw.	113
76	(electronic adj mail$).tw.	2105
77	e-mail$.tw.	26073
78	listserv$.tw.	3250
79	(compact adj disk).tw.	310
80	DVD.tw.	4799
81	(USB adj key?).tw.	21
82	workshop?.tw.	111795
83	mail$.tw.	115777
84	(fax$ or facsimile?).tw.	5798
85	transmit$.tw.	422093
86	(USB adj drive?).tw.	45
87	((educat$ or train$ or learn$ or teach$) adj program?).tw.	200869
88	((educat$ or teach$ or learn$ or instruction$ or train$) and course?).tw.	212371
89	disseminat$.tw.	366495
90	sent.tw.	190538
91	campaign$.tw.	126990
92	Postal Service/	7150
93	50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92	2990016
94	21 and 49 and 93	26938
95	limit 94 to randomized controlled trial	1663
96	limit 95 to english language	1637
97	limit 96 to human	1616
98	limit 97 to yr="2015 -Current"	856
99	remove duplicates from 98	664

Appendix B: Systematic review data extraction form

Suggested citation: Cochrane Effective Practice and Organisation of Care (EPOC). Data collection form. EPOC Resources for review authors, 2017. epoc.cochrane.org/resources/epoc-specific-resources-review-authors [accessed DD Month YYYY]

THE COCHRANE COLLABORATION®

Data collection form

Intervention review –
Randomised trials and non-randomised trials

This form can be used as a guide for developing your own data extraction form. Sections can be expanded and added, and irrelevant sections can be removed. It is difficult to design a single form that meets the needs of all reviews, so it is important to consider carefully the information you need to collect, and design your form accordingly. Information included on this form should be comprehensive, and may be used in the text of your review, 'Characteristics of included studies' table, risk of bias assessment, and statistical analysis.

Notes on using a data extraction form:

- Be consistent in the order and style you use to describe the information for each included study.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.
- Include any instructions and decision rules on the data collection form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.
- You will need to protect the document in order to use the form fields (Tools / Protect document)

Review title or ID

Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*

Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*

Notes:

1… General Information

1. **Date form completed** *(dd/mm/yyyy)*	
2. **Name/ID of person extracting data**	
3. **Report title** *(title of paper/ abstract/ report that data are extracted from)*	
4. **Report ID** *(if there are multiple reports of this study)*	
5. **Reference details**	
6. **Report author contact details**	

7. **Publication type** *(e.g. full report, abstract, letter)*	
8. **Study funding source** *(including role of funders)*	
Possible conflicts of interest *(for study authors)*	
9. **Notes:**	

2... Eligibility

Study Characteristics	**Review Inclusion Criteria** *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	**Yes/ No / Unclear**	**Location in text** *(pg & ¶/fig/table)*
10. **Type of study**	Randomised trial	...	
	Non-randomised trial	...	
	Controlled before-after study • Contemporaneous data collection • At least 2 intervention and 2 control clusters	...	
	Interrupted time series OR Repeated measures study • At least 3 timepoints before and 3 after the intervention • Clearly defined intervention point	... ...	
	Other design (specify):	...	
11. **Participants**		...	
12. **Types of intervention**		...	
13. **Types of outcome measures**		...	
14. **Decision:**	...		
15. **Reason for exclusion**			
16. **Notes:**			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3... Population and setting

	Description *Include comparative information for each group (i.e. intervention and controls) if available*	**Location in text** *(pg & ¶/fig/table)*
17. **Population description** *(from which study participants are drawn)*		
18. **Setting** *(including location and social context)*		
19. **Inclusion criteria**		
20. **Exclusion criteria**		
21. **Method/s of recruitment of participants**		
22. **Notes:**		

4... Methods

	Descriptions as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
23. **Aim of study**		
24. **Design** *(e.g. parallel, crossover, non-RCT)*		
25. **Unit of allocation** *(by individuals, cluster/ groups or body parts)*		
26. **Start date**		
27. **End date**		
28. **Duration of participation** *(from recruitment to last follow-up)*		
29. **Notes:**		

5... Risk of Bias assessment

See Chapter 8 of the Cochrane Handbook. Additional domains may be required for non-randomised studies.

Domain	**Risk of bias** *Low/ High/Unclear*	**Support for judgement**	**Location in text** *(pg & ¶/fig/table)*
30. **Random sequence generation** *(selection bias)*	...		
31. **Allocation concealment** *(selection bias)*	...		

Domain	Risk of bias *Low/ High/Unclear*	Support for judgement	Location in text *(pg & ¶/fig/table)*
32. **Blinding of participants and personnel** *(performance bias)*	…	**Outcome group:** **All/**	
(if required)	…	**Outcome group:**	
33. **Blinding of outcome assessment** *(detection bias)*	…	**Outcome group:** **All/**	
(if required)	…	**Outcome group:**	
34. **Incomplete outcome data** *(attrition bias)*	…		
35. **Selective outcome reporting?** *(reporting bias)*	…		
36. **Other bias**	…		
37. **Notes:**			

6... Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
38. **Total no. randomised** *(or total pop. at start of study for NRCTs)*		
39. **Clusters** *(if applicable, no., type, no. people per cluster)*		
40. **Baseline imbalances**		
41. **Withdrawals and exclusions** *(if not provided below by outcome)*		
42. **Age**		
43. **Sex**		
44. **Race/Ethnicity**		
45. **Severity of illness**		
46. **Co-morbidities**		
47. **Other treatment received** *(additional to study intervention)*		
48. **Other relevant sociodemographics**		
49. **Subgroups measured**		
50. **Subgroups reported**		
51. **Notes:**		

7... Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
52. **Group name**		
53. **No. randomised to group** *(specify whether no. people or clusters)*		
54. **Description** *(include sufficient detail for replication, e.g. content, dose, components; if it is a natural experiment, describe the pre-intervention)*		
55. **Duration of treatment period**		
56. **Timing** *(e.g. frequency, duration of each episode)*		
57. **Delivery** *(e.g. mechanism, medium, intensity, fidelity)*		
58. **Providers** *(e.g. no., profession, training, ethnicity etc. if relevant)*		
59. **Co-interventions**		
60. **Economic variables** *(i.e. intervention cost, changes in other costs as result of intervention)*		
61. **Resource requirements to replicate intervention** *(e.g. staff numbers, cold chain, equipment)*		
62. **Notes:**		

8... Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
63. **Outcome name**		
64. **Time points measured** *(specify whether from start or end of intervention)*		
65. **Time points reported**		

	Description as stated in report/paper		Location in text *(pg & ¶/fig/table)*
66. **Outcome definition** *(with diagnostic criteria if relevant and note whether the outcome is desirable or undesirable if this is not obvious)*			
67. **Person measuring/ reporting**			
68. **Unit of measurement** *(if relevant)*			
69. **Scales: upper and lower limits** *(indicate whether high or low score is good)*			
70. **Is outcome/tool validated?**	... *Yes/No/Unclear*		
71. **Imputation of missing data** *(e.g. assumptions made for ITT analysis)*			
72. **Assumed risk estimate** *(e.g. baseline or population risk noted in Background)*			
73. **Notes:**			

9... Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

For randomised or non-randomised trial - Dichotomous outcome

	Description as stated in report/paper				Location in text *(pg & ¶/fig/table)*
74. **Comparison**					
75. **Outcome**					
76. **Subgroup**					
77. **Time point** *(specify whether from start or end of intervention)*					
78. **Results** *Note whether:* **...** *post-intervention OR* **...** *change from baseline And whether* **...** *Adjusted OR* **...***Unadjusted*	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
79. **Baseline data**	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
80. **No. missing participants and reasons**					

10. Applicability

158. **Have important populations been excluded from the study?** *(consider disadvantaged populations, and possible differences in the intervention effect)*	... *Yes/No/Unclear*	
159. **Is the intervention likely to be aimed at disadvantaged groups?** *(e.g. lower socioeconomic groups)*	... *Yes/No/Unclear*	
160. **Does the study directly address the review question?** *(any issues of partial or indirect applicability)*	... *Yes/No/Unclear*	
161. **Notes:**		

11. Other information

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
162. **Key conclusions of study authors**		
163. **References to other relevant studies**		
164. **Correspondence required for further study information** *(what and from whom)*		
165. **Further study information requested** *(from whom, what and when)*		
166. **Correspondence received** *(from whom, what and when)*		
167. **Notes:**		

Appendix C: First draft of the intervention (Version 1 & 2)

Version 1: The detailed version (2 pages – four-sided)

The University Of Sheffield.

TRAINS Trial

To:
- GPs
- Clinical Commissioning Groups

The University of Sheffield
School of Health and Related Research
Regent Court
30 Regent St
Sheffield
S1 4DA

15 March 2021

Dear GPs and their commissioners,

Please Read This Important Information

"The Importance of Children with Asthma taking their Preventer Medications during Summer Holiday; Evidence-based Recommendation"

For school-age children with asthma, there is a marked increase in unscheduled medical care after they return to school in September. It is thought that is partially due to children not taking their asthma preventer medication during the school holidays (Julious et al., 2011).

In England and Scotland, there is a noticeable increase in the number of unscheduled visits to GPs by school-aged children with asthma in September associated with the return back to school after the holidays in England. The same pattern is seen in August for Scotland as they go back to school earlier than English schools. (as shown in figure A&B).

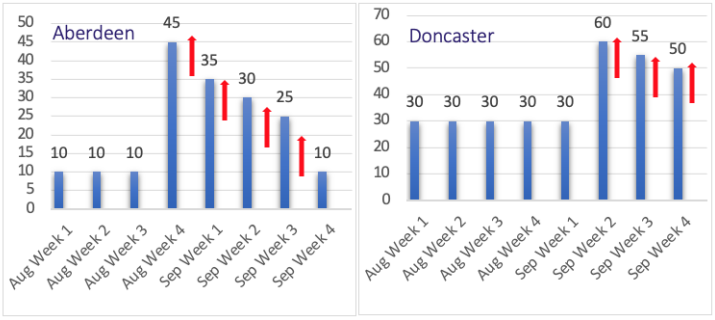


Figure A&B: Weekly hospital admission due to asthma for school-aged children (5–16 years) in England and Scotland. (Julious, Osman and Jiwa, 2007)

Why did this information important?

"From the previous studies and statistics, we conclude that a reminder letter from general practices to parents of child with asthma could lead to many benefits."

- "Since *Summer is coming, it's the time to send a reminder"*

- "We include a reminder letter sheet that you could send it to child's parents. (Please see next page)."

For more information on The PLEASANT Trial please go to
https://www.sheffield.ac.uk/scharr/research/centres/ctru/pleasant

For any queries please don't hesitate to contact us at:

rahalyami1@sheffield.ac.uk

References:

Julious, S. A. *et al.* (2011) 'Seasonality of medical contacts in school-aged children with asthma: association with school holidays', *Public Health*. Elsevier, 125(11), pp. 769–776.

Julious, S. A. *et al.* (2016) 'PLEASANT: Preventing and lessening exacerbations of Asthma in school-age children associated with a new term-a cluster randomised controlled trial and economic evaluation', *Health Technology Assessment*, 20(93), pp. 1–154. doi: 10.3310/hta20930.

Julious, S. A. *et al.* (2018) 'Open-label, cluster randomised controlled trial and economic evaluation of a brief letter from a GP on unscheduled medical contacts associated with the start of the school year: The PLEASANT trial', *BMJ Open*, 8(4), pp. 1–11. doi: 10.1136/bmjopen-2017-017367.

Julious, S. A., Osman, L. M. and Jiwa, M. (2007) 'Increases in asthma hospital admissions associated with the end of the summer vacation for school-age children with asthma in two cities from England and Scotland', *Public Health*, 121, pp. 482–484. doi: 10.1016/j.puhe.2006.11.011.

GP letterhead

< Address line 1>
< Address line 2>
< Address line 3>
< Address line 4>

<Insert Date>

Dear Parent

Please read this important letter regarding your child's asthma

It is really important that your child continues to take their asthma medication during the summer holidays. Returning to school is a time when asthma can get worse and make children and young people with asthma poorly. This may be due to contact with infections at the start of the new school year.

To reduce the chances of getting poorly when they return to school, your child should continue to take their asthma medication as prescribed by their GP or practice nurse. If your child has stopped taking their medication over the summer holidays it is important to start it again as soon as possible. If they are short of medication, or you are not sure of the proper dose, please get in touch with the practice.

Yours sincerely

<Name of Doctor>

Version 2: The brief version (1 page – two-sided)

The University Of Sheffield.

Please Read

The Importance of Children with Asthma taking their Preventer Medications during Summer Holiday; Evidence-based Recommendation

For school-age children with asthma, there is a marked increase in unscheduled medical care after they return to school in September. It is thought that is partially due to children not taking their asthma preventer medication during the school holidays (Julious et al., 2011).

In England and Scotland, there is a noticeable increase in the number of unscheduled visits to GPs by school-aged children with asthma in September associated with the return back to school after the holidays in England. The same pattern is seen in August for Scotland as they go back to school earlier than English schools (Julious *et al.*, 2011).

So, what the pervious information led to?

These data led to the **PLEASANT** study *(**P**reventing and **L**essening **E**xacerbations of **A**sthma in **S**chool-age children **A**ssociated with a **N**ew **T**erm)* (Julious *et al.*, 2016).

PLEASANT was a cluster randomised trial to evaluate whether a letter sent from a GP at the start of the summer vacation reminding parents of children with asthma of the necessity of continuing to take their medication during the summer holiday. The study included 12,179 school-age children in 141 general practices (71 on intervention, and 70 on the control) in England and Wales(Julious *et al.*, 2018).

What did the study find?

The letter resulted in:

- *increased prescription uptake in August by 30%*.
- *reduced the unscheduled medical contacts after the return to school in September*.
- *Cost saving by 36£ per child.*

Recommendation:

"From the previous studies and statistics, and since the summer is coming soon, we conclude that a reminder letter from general practices to parents of child with asthma could lead to many benefits."

For more information on The PLEASANT Trial please go to
https://www.sheffield.ac.uk/scharr/research/centres/ctru/pleasant

To download the reminder letter: scan the code down or go to the above website then scroll down to – Downloads – then choose the last file named **Intervention letter (DOC, 16KB)**

You can contact us with any quires at:
rahalyami1@sheffield.ac.uk

References:

Julious, S. A. *et al.* (2011) 'Seasonality of medical contacts in school-aged children with asthma: association with school holidays', *Public Health*. Elsevier, 125(11), pp. 769–776.
Julious, S. A. *et al.* (2016) 'PLEASANT: Preventing and lessening exacerbations of Asthma in school-age children associated with a new term-a cluster randomised controlled trial and economic evaluation', *Health Technology Assessment*, 20(93), pp. 1–154. doi: 10.3310/hta20930.
Julious, S. A. *et al.* (2018) 'Open-label, cluster randomised controlled trial and economic evaluation of a brief letter from a GP on unscheduled medical contacts associated with the start of the school year: The PLEASANT trial', *BMJ Open*, 8(4), pp. 1–11. doi: 10.1136/bmjopen-2017-017367.

Appendix D: The revised draft of the Intervention (the brief version)

The University Of Sheffield.

Please Read

The importance of children with asthma taking their preventer medications during summer holiday; Evidence-based recommendation

In England and Scotland, there is a marked increase in unscheduled medical care for school-age children with asthma after they return to school in September. It is thought this is partially due to children not taking their asthma preventer medication during the summer holidays (Julious et al., 2011).

How can we tackle the problem?

The PLEASANT study *(**P**reventing and **L**essening **E**xacerbations of **A**sthma in **S**chool-age children **A**ssociated with a **N**ew **T**erm):*

PLEASANT was a cluster randomised trial conducted in 12,179 school-age children in 141 general practices in England and Wales (Julious *et al.*, 2018).

What did the study find?

This study found that a simple reminder letter sent from the GP practice to a parent with a child with asthma informing them of the importance of taking asthma medication prior to the start of the school year resulted in:

- √ ***Increased*** *prescription uptake in August by 30%.*
- √ ***A reduction*** *in the unscheduled medical contacts after the return to school in September.*
- √ ***Cost savings*** *by £36 per child.*

Recommendation:

As summer is approaching, a reminder letter from general practices to parents of children with asthma could lead to these benefits.

For more information on The PLEASANT Trial, please go to:
https://www.sheffield.ac.uk/scharr/research/centres/ctru/pleasant

To download the reminder letter: scan the code below go to the above website then scroll down to - Downloads - then choose the last file named **Intervention letter (DOC, 16KB)**

Reminder letter

Reminder text

You can contact us with any queries at:
rahalyami1@sheffield.ac.uk

References:

Julious, S. A. *et al.* (2011) 'Seasonality of medical contacts in school-aged children with asthma: association with school holidays', *Public Health*. Elsevier, 125(11), pp. 769-776.

Julious, S. A. *et al.* (2016) 'PLEASANT: Preventing and lessening exacerbations of Asthma in school-age children associated with a new term-a cluster randomised controlled trial and economic evaluation', *Health Technology Assessment*, 20(93), pp. 1-154. doi: 10.3310/hta20930.

Julious, S. A. *et al.* (2018) 'Open-label, cluster randomised controlled trial and economic evaluation of a brief letter from a GP on unscheduled medical contacts associated with the start of the school year: The PLEASANT trial', *BMJ Open*, 8(4), pp. 1-11. doi: 10.1136/bmjopen-2017-017367.

Appendix E: The Final design of intervention
Letter to GPs

The University Of Sheffield.

The University of Sheffield
School of Health and
Related Research
Regent Court
30 Regent St
Sheffield
S1 4DA

To The Practice Manager and Asthma Lead,

We can help you to tackle peaks in asthma and improve outcomes for your young patients this summer.

As the asthma lead for your practice, I am writing to you with recommendations that will help you and your GP practice to reduce serious, asthma-related exacerbations in the young patients with asthma that you support.

Did you know?

Summer holidays are key for young people with asthma

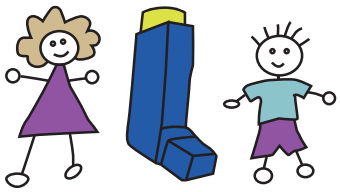
The summer holidays are a crucial time for children with asthma to take their preventer medication ahead of the return to school, yet it often gets forgotten. With your help, a simple reminder to the parents of your young patients with asthma can **significantly reduce the number of serious medical attendances, hospital admissions and the associated costs**. Our recent University of Sheffield study of young patients with asthma supports this, as you'll see below.

How can we help you?

In one simple step

We are recommending that asthma leads at GP surgeries across England send a reminder letter or SMS text **in July.** This is to remind the parents or guardians of all school-age children with asthma to take their asthma medication during the summer break.

We've attached a sample reminder letter and SMS text.



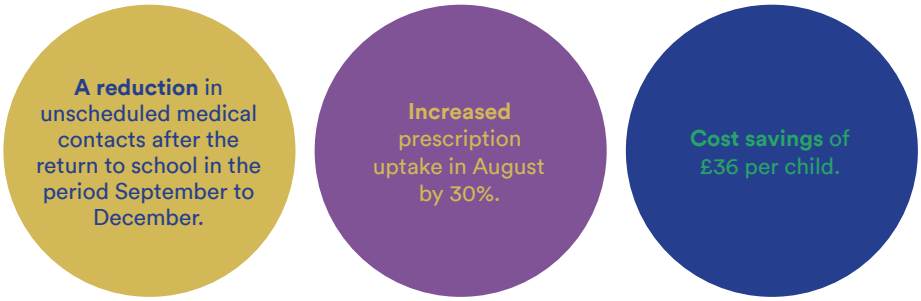
PLEASANT

What did our asthma study show?

Significant benefits of summer parent reminders

Initial findings of our asthma study showed a marked increase in unscheduled medical care for school-age children with asthma after they returned to school in September. It is thought that this is partially due to children not taking their asthma preventer medication during the summer holidays.

Our study found that a simple reminder letter sent by GPs to parents and guardians of children with asthma, reminding them to take their asthma medication during the summer holidays has resulted in:



Who can I contact about the asthma study?

If you would like more information about our asthma study or have any questions, please contact us at:
rahalyami1@sheffield.ac.uk

With one simple reminder message, you and your GP surgery can enable your young patients to manage their asthma better, ahead of the return to school.

To find out more about our asthma study known as **PLEASANT**, please read the attached leaflet or visit:
https://www.sheffield.ac.uk/scharr/research/centres/ctru/pleasant

Yours faithfully,

Professor Steven A. Julious
The University of Sheffield

Reference:

Julious, S.A., Horspool, M.J., Davis, S., Franklin, M., Smithson, W.H., Norman, P., Simpson, R.M., Elphick, H., Bortolami, O. and Cooper, C., 2018. Open-label, cluster randomised controlled trial and economic evaluation of a brief letter from a GP on unscheduled medical contacts associated with the start of the school year: the PLEASANT trial. BMJ open, 8(4).

Supported leaflet attached to the letter

How can our findings help you and your patients with asthma?

In one simple step

We are recommending that asthma leads at GP surgeries across England send a reminder letter or SMS text **in July**. This is to remind the parents or guardians of all school-age children with asthma to take their asthma medication during the summer break. If you'

Click to download the letter or download the SMS text template.

Who can I contact about this asthma study?

If you would like more information or have any questions about our asthma study, please contact us at rahalyami1@sheffield.ac.uk

With one simple reminder message, you and your GP surgery can enable your young patients to manage their asthma better ahead of the return to school.

Publications

Julious SA, Horspool MJ, Davis S, Franklin M, Smithson WH, Norman P et al (2018). Open-label, cluster randomised controlled trial and economic evaluation of a brief letter from a GP on unscheduled medical contacts associated with the start of the school year: the PLEASANT trial. BMJ Open, 8(4), e017367.

Franklin M, Davis S, Horspool M, Kua WS & Julious S (2017). Economic Evaluations Alongside Efficient Study Designs Using Large Observational Datasets: the PLEASANT Trial Case Study. PharmacoEconomics, 35(5), 561-573.

Julious SA, Horspool MJ, Davis S, Bradburn M, Norman P, Shephard N, Cooper CL et al (2017) PLEASANT: Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term - a cluster randomised controlled trial and economic evaluation.. Health Technology Assessment, 20(93), 1-154.

PLEASANT

Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term

Information for asthma leads and practice managers in GP surgeries.

Many thanks for your interest in our University of Sheffield study of young patients with asthma.

If you're reading this leaflet, you've probably already received a letter from us highlighting how we can help you to reduce peaks in asthma for your young patients this summer.

This leaflet is for asthma leads like you across England, who'd like to know more about the study behind our summer awareness campaign for your young patients with asthma.

Our findings show that with your help, a simple reminder to the parents or guardians of your young patients with asthma can **reduce unscheduled care** when they return to school. Read on to find out more.

Asthma in young people – four findings to help you and them

The summer holidays are a crucial time for children with asthma to take their preventer medication ahead of the return to school, yet it often gets forgotten.

- **The return to school in September is a time when asthma gets worse for children** and there's an increase in medical help. This may be due to their contact with infections as they begin to mix with children in school at the start of the new school year.
- Our research shows **that children with asthma are twice as likely to see their doctor after the school return** compared to children without asthma.
- During the summer holidays, there's a significant drop in the number of prescriptions for asthma medication that are collected. **Children that aren't collecting their prescriptions are more likely to see their doctor.**
- **Communications which encourage school-age children to continue their prescribed medication, can make a real difference in helping them to manage their asthma.**

What did our asthma study show?

Significant benefits of summer parent reminders.

We carried out a trial of 12,179 school-age children in 141 GP practices across England and Wales, chosen at random.
Our study found that a simple reminder letter sent by the family GP to parents or guardians of children with asthma, asking them to make sure their child takes their preventer medication during the summer holidays, has resulted in:

A reduction in unscheduled medical contacts after the return to school in the period September to December.

Increased prescription uptake in August by 30%.

Cost savings of £36 per child.

To find out more about our asthma study known as **PLEASANT**, please visit: https://www.sheffield.ac.uk/scharr/research/centres/ctru/pleasant

A suggested reminder letter template attached to the letter

GP letterhead

< Address line 1>
< Address line 2>
< Address line 3>
< Address line 4>

<Insert Date>

Dear Parent

This summer holiday you can help prevent your child's asthma

Did you know that the summer holidays are a crucial time for continuing your child's asthma medication?

The return to school in September is a time when asthma often gets worse for young people. This may be due to contact with infections at the start of the new school year. But don't worry, act now and you can make the difference this summer.

How can I help prevent my child's asthma?

This summer, simply make sure you're child continues to take their asthma medication, as per their normal prescription.

What if my child has stopped taking their medication?

If your child has stopped taking their medication over the summer holidays, start it again as soon as possible. If they're short of medication, or you're not sure of the proper dose, please get in touch with us.

You can reduce the chances of your child getting poorly and help them have a safer return to school.

Yours sincerely

<Name of Doctor>

A suggested SMS text reminder template attached to the letter

SMS Text (245 characters)

Reminder from your GP surgery: During the summer holidays, please make sure your child takes their asthma medication as per their usual prescription. You can help them have a safer return to school and reduce the chances of them getting poorly.

Email to GPs

Subject: This summer help manage asthma in your young patients

To the Practice Manager and Asthma Lead,

I am writing to you with recommendations that will help you and your GP practice to reduce serious, asthma-related exacerbations in your young patients with asthma, ahead of the return to school. (Please READ the attached letter)

With one simple reminder message this summer, you and your GP surgery can enable your young patients to manage their asthma better.

Here's why:

- The return to school in September is a time when asthma gets worse for children and there's an increase in medical help.
- During the summer holidays, there's a significant drop in the number of prescriptions for asthma medication that are collected.
- The summer holidays are a crucial time for children with asthma to take their preventer medication ahead of the return to school, yet often it gets forgotten.

How can we help you?

We are recommending that asthma leads like you at GP surgeries across England send a simple reminder letter or SMS text **in July.** This is to remind the parents or guardians of all school-age children with asthma to take their asthma medication during the summer break.

We've attached a sample reminder letter and SMS text (see attached). Alternatively click to download the letter or download the SMS text template.

With your help, this simple reminder to the parents of your young patients with asthma can **significantly reduce the number of serious medical attendances, hospital admissions and the associated costs**. Our recent University of Sheffield study (PLEASANT) of young patients with asthma supports this. You can find out more by reading the attached leaflet or visiting: https://www.sheffield.ac.uk/scharr/research/centres/ctru/pleasant

Who can you contact about our asthma study?

If you would like more information about our asthma study or have any questions, please contact us at: rahalyami1@sheffield.ac.uk

With one reminder, you and your GP surgery can make a difference in helping your young patients to manage their asthma better and have a safer return to school.

Yours faithfully,

Steven

Professor Steven A. Julious

The University of Sheffield

Appendix F: Asthma diagnosis code & asthma medications

1. Included asthma diagnosis code

Term	
1.	Intrinsic asthma without status asthmaticus
2.	Detergent asthma
3.	Wood asthma
4.	Occupational asthma
5.	Life threatening acute exacerbation of intrinsic asthma
6.	Extrinsic asthma without status asthmaticus
7.	Life threatening acute exacerbation of allergic asthma
8.	Emergency asthma patient visit since last encounter
9.	H/O: asthma
10.	Asthma causing night waking
11.	Asthma disturbs sleep weekly
12.	Asthma disturbs sleep frequently
13.	Asthma not disturbing sleep
14.	Asthma disturbing sleep
15.	Asthma never disturbs sleep
16.	Asthma limiting activities
17.	Asthma not limiting activities
18.	Asthma management
19.	Asthma severity
20.	Asthma prophylactic medication used
21.	Emergency asthma admission since last encounter
22.	Asthma restricts exercise
23.	Asthma sometimes restricts exercise
24.	Asthma severely restricts exercise
25.	Asthma screening
26.	Asthma never restricts exercise
27.	Asthma control step 0
28.	Asthma control step 1
29.	Asthma control step 2
30.	Asthma control step 3
31.	Asthma control step 4
32.	Asthma control step 5
33.	Emergency hospital admission for asthma
34.	Seen in asthma clinic
35.	Attends asthma monitoring
36.	Asthma monitoring refused
37.	Asthma monitor offer default

38. Asthma monitoring deleted
39. Patient in asthma study
40. Chronic asthmatic bronchitis
41. Bronchial asthma
42. Asthma
43. Extrinsic asthma
44. Intrinsic asthma NOS
45. Mixed asthma
46. Asthma unspecified
47. Brittle asthma
48. Childhood asthma
49. Late onset asthma
50. Late-onset asthma
51. Acute exacerbation of allergic asthma
52. Allergic asthma NEC
53. Hay fever with asthma
54. Pollen asthma
55. Acute exacerbation of intrinsic asthma
56. Intrinsic asthma
57. Life threatening acute exacerbation of asthma
58. Asthma attack
59. Asthma monitored
60. Asthma monitoring check done
61. Asthma NOS
62. Asthma attack NOS
63. Asthma monitoring
64. Acute exacerbation of asthma
65. Asthma - currently active
66. Asthma causes daytime symptoms 1 to 2 times per week
67. Asthma causes daytime symptoms 1 to 2 times per month
68. Asthma causes daytime symptoms most days
69. Asthma causes night symptoms 1 to 2 times per month
70. Asthma limits walking on the flat
71. Asthma limits walking up hills or stairs
72. Asthma never causes daytime symptoms
73. Number of asthma exacerbations in past year
74. Mild asthma
75. Moderate asthma
76. Occasional asthma
77. Severe asthma
78. Asthma treatment compliance unsatisfactory

79. Asthma treatment compliance satisfactory
80. Asthma daytime symptoms
81. Allergic asthma
82. Change in asthma management plan
83. Step down change in asthma management plan
84. Step up change in asthma management plan
85. Absent from work or school due to asthma
86. Asthma monitoring due
87. Asthma annual review
88. Asthma medication review
89. Asthma follow-up
90. Suspected asthma
91. Asthma night-time symptoms
92. Cardiac asthma
93. Asthma trigger
94. Health education - asthma
95. Asthma monitoring by nurse
96. Asthma monitoring by doctor
97. Asthma confirmed
98. Asthma clinical management plan
99. Referral to asthma clinic
100. Asthma monitoring using asthma symptom diary
101. Use of asthma symptom diary
102. Moderate acute exacerbation of asthma
103. Exacerbation of allergic asthma
104. Asthma monitoring admin.NOS
105. Asthma monitoring administration
106. Asthma clinic administration
107. Acute severe exacerbation of asthma
108. Sequoiosis (red-cedar asthma)
109. Did not attend asthma clinic
110. Does not have asthma management plan
111. Asthma outreach clinic
112. Asthma trigger: animals
113. Asthma monitoring call first letter
114. Asthma monitoring call second letter
115. Asthma monitoring call third letter
116. Asthma monitoring call telephone invite
117. Asthma monitoring call verbal invite
118. Royal College of Physicians asthma assessment
119. Asthma trigger - damp

120. Asthma trigger - cold air
121. Asthma trigger - emotion
122. Asthma trigger - respiratory infection
123. Asthma trigger - seasonal
124. Exercise-induced asthma
125. Exercise induced asthma
126. Allergic atopic asthma
127. Further asthma - drug prevention
128. Hay fever with asthma
129. Asthma stable < 3 months
130. Asthma stable > 3 months
131. Asthma control unsatisfactory
132. Extrinsic asthma - atopy
133. [RFC] Asthma
134. [RFC] Asthma
135. Aspirin-induced asthma
136. Occupational asthma
137. Referral to Asthma clinic
138. Work aggravated asthma
139. Asthma control test score
140. Asthma Control Questionnaire score
141. Mini AQLQ (Asthma Quality of Life Questionnaire) score
142. Under care of asthma specialist nurse
143. Patient has a written asthma personal action plan
144. Health education - asthma self management
145. Health education - structured asthma discussion
146. Asthma causes night time symptoms 1 to 2 times per week
147. Asthma causes symptoms most nights
148. Asthma limits activities 1 to 2 times per month
149. Asthma limits activities 1 to 2 times per week
150. Asthma limits activities most days
151. Asthma trigger - airborne dust
152. Asthma trigger - exercise
153. Asthma trigger - pollen
154. Asthma trigger - tobacco smoke
155. Asthma trigger - warm air
156. Health education - structured patient focused asthma discussion
157. Asthma review using Royal College of Physicians three questions
158. Royal College of Physicians asthma assessment three questions score
159. Asthma never causes night symptoms
160. Seen in school asthma clinic

161. Staff group: Nursing - Asthma and Respiratory Nursing/Liaison
162. Asthma causes daytime symptoms more than weekly, less than daily
163. Asthma causes daytime asthma symptoms daily
164. Asthma causes daytime asthma symptoms less than weekly
165. Asthma causes night time symptoms less than 2 times per month
166. Asthma causes night time symp more than 2 times a month,not wkly
167. Asthma causes night time asthma symptoms weekly or more often
168. Number of days absent from school due to asthma in past 6 months
169. Frequent night time asthma symptoms
170. Infrequent asthma exacerbations
171. Frequent asthma exacerbations
172. Asthma monitoring in primary care
173. Asthma monitoring in secondary care
174. Follow-up asthma assessment
175. Date of asthma diagnosis
176. Asthma clinical management plan no longer in place
177. No change in asthma management plan
178. Review of patient at risk of asthma
179. Access to online patient asthma education given
180. Asthma monitoring invitation SMS (short message service) text message
181. Asthma monitoring SMS (short message service) text message first invitation
182. Asthma monitoring SMS (short message service) text message second invitation
183. Asthma monitoring SMS (short message service) text message third invitation
184. Asthma-chronic obstructive pulmonary disease overlap syndrome
185. Keele ENHANCE trial - asthma review
186. Manchester triage - Asthma
187. Difficult asthma
188. Acute infective exacerbation of asthma
189. Acute non-infective exacerbation of asthma
190. Asthma self-management plan review
191. Asthma self-management plan agreed
192. Asthma trigger - perfume
193. Chronic asthma with fixed airflow obstruction
194. Asthma management plan declined
195. Childhood Asthma Control Test score
196. Asthma monitoring invitation email
197. Review of patient at risk of asthma
198. Telehealth asthma monitoring
199. Asthma action plan
200. At risk of severe asthma exacerbation
201. Severe asthma exacerbation risk assessment

202. Millers' asthma
203. Exercise induced asthma
204. Bakers' asthma
205. Industrial asthma
206. Drug-induced asthma
207. History of asthma
208. Asthmatic
209. Late-onset asthma
210. Asthmatic pulmonary eosinophilia
211. Non-allergic asthma
212. Exacerbation of asthma
213. Asthma control steps
214. Asthma monitoring call
215. Asthma monitoring status
216. Eosinophilic asthma
217. Asthma finding
218. Atopic asthma
219. Nocturnal asthma
220. Asthma education
221. Asthmatic bronchitis
222. Asthma care
223. Cough variant asthma
224. Non-IgE mediated allergic asthma
225. IgE-mediated allergic asthma
226. IgE mediated asthma
227. Exacerbation of intermittent asthma
228. Mild persistent asthma
229. Moderate persistent asthma
230. Intermittent asthma
231. Mild intermittent asthma
232. History of aspirin-sensitive asthma with nasal polyp
233. Acute exacerbation of chronic asthmatic bronchitis
234. Asthma nurse specialist
235. Seasonal asthma
236. ACQ - Asthma control questionnaire
237. Education about asthma self management
238. Did not attend asthma review
239. Asthma clinic
240. Exacerbation of mild persistent asthma
241. Exacerbation of moderate persistent asthma
242. Uncomplicated mild persistent asthma

243. Acute severe exacerbation of severe persistent asthma
244. Acute severe exacerbation of allergic asthma
245. Acute severe exacerbation of intrinsic asthma
246. Recent asthma management
247. Asthma action care planning
248. Acute severe refractory exacerbation of asthma
249. Acute severe asthma
250. Asthma with irreversible airway obstruction
251. Intermittent asthma well controlled
252. Intermittent asthma uncontrolled
253. Acute exacerbation of chronic obstructive airways disease with asthma
254. Asthma action plan not done
255. Acute exacerbation of mild persistent asthma
256. Asthma trigger - respiratory infection
257. Acute exacerbation of moderate persistent asthma
258. Asthma trigger - seasonal
259. Asthma trigger - cold air
260. Asthma trigger - damp
261. Asthma trigger - emotion
262. RCP (Royal College of Physicians) asthma assessment
263. Asthma trigger - airborne dust
264. Asthma trigger - exercise
265. Asthma trigger - pollen
266. Asthma trigger - tobacco smoke
267. Asthma trigger - warm air
268. Asthma trigger - wind
269. No asthma trigger identified by subject
270. Assessment using Childhood Asthma Control Test
271. Steroid dependent asthma
272. Severe controlled persistent asthma
273. Severe persistent asthma uncontrolled co-occurrent with allergic rhinitis
274. Severe uncontrolled persistent asthma
275. Mild persistent allergic asthma
276. Mild persistent asthma controlled
277. Mild persistent asthma uncontrolled
278. Mild persistent asthma uncontrolled co-occurrent with allergic rhinitis
279. Moderate persistent asthma uncontrolled
280. Chronic obstructive asthma co-occurrent with acute exacerbation of asthma
281. Asthma-COPD overlap syndrome (ACOS)
282. ACOS - asthma-chronic obstructive pulmonary disease overlap syndrome
283. Oral steroid-dependent asthma

284. Asthma nurse specialist telephone encounter
285. Acute asthma
286. Asthma control test
287. Asthma control questionnaire
288. Childhood Asthma Control Test
289. ACQ (Asthma Control Questionnaire) score
290. Assessment using Asthma Control Questionnaire
291. Refuses asthma monitoring
292. Severe asthma with fungal sensitisation
293. QOF (Quality and Outcomes Framework) asthma quality indicator-related care invitation
294. QOF (Quality and Outcomes Framework) asthma quality indicator-related care invitation using preferred method of communication
295. Registration for access to online asthma self-management application
296. Declined to register for access to online asthma self-management application
297. Exacerbation of allergic asthma due to infection
298. Asthma never causes night symptoms
299. Allergic asthma without status asthmaticus
300. Thunderstorm asthma
301. Intermittent allergic asthma

2. Included asthma-related medication for school-age children with asthma.

Term from EMIS

1. Accolate 20mg tablets (AstraZeneca UK Ltd)
2. Aerivio Spiromax 50micrograms/dose / 500micrograms/dose dry powder inhaler (Teva UK Ltd)
3. AeroBec 100 Autohaler (Meda Pharmaceuticals Ltd)
4. AeroBec 50 Autohaler (Meda Pharmaceuticals Ltd)
5. AeroBec Forte 250 Autohaler (Meda Pharmaceuticals Ltd)
6. Aerocrom inhaler (Castlemead Healthcare Ltd)
7. Aerocrom Syncroner with spacer (Castlemead Healthcare Ltd)
8. Aerolin 100micrograms/dose Autohaler (3M Health Care Ltd)
9. Aerolin 400 Aerosol inhalation 100 mcg/metered inhalation
10. Aerolin Auto Aerosol inhalation 100 micrograms/metered dose
11. Aerolin Autohaler Breath-Actuated Inhaler (Cfc-Free) 100 micrograms/dose
12. AirFluSal 25micrograms/dose / 125micrograms/dose inhaler (Sandoz Ltd)
13. AirFluSal 25micrograms/dose / 250micrograms/dose inhaler (Sandoz Ltd)
14. AirFluSal Forspiro 50micrograms/dose / 500micrograms/dose dry powder inhaler (Sandoz Ltd)
15. Airomir 100micrograms/dose Autohaler (Teva UK Ltd)
16. Airomir 100micrograms/dose inhaler (Teva UK Ltd)
17. AirSalb 100micrograms/dose inhaler CFC free (Sandoz Ltd)
18. Aloflute 25micrograms/dose / 125micrograms/dose inhaler (Mylan)
19. Aloflute 25micrograms/dose / 250micrograms/dose inhaler (Mylan)
20. Alupent 10mg/5ml syrup (Boehringer Ingelheim Ltd)
21. Alupent 20mg tablets (Boehringer Ingelheim Ltd)
22. Alvesco 160 inhaler (AstraZeneca UK Ltd)
23. Alvesco 80 inhaler (AstraZeneca UK Ltd)
24. Alvesco Cfc-free inhaler 160 micrograms/actuation, 120 doses
25. Alvesco Cfc-free inhaler 160 micrograms/actuation, 60 doses
26. Aminophylline 100mg tablets
27. Aminophylline 225mg modified-release tablets
28. Aminophylline 250mg/10ml solution for injection ampoules
29. Aminophylline hydrate 225mg modified-release tablets
30. Aminophylline hydrate 350mg modified-release tablets
31. Aminophylline Injection 25 mg/1 ml
32. Aminophylline Injection 250 mg/1 ml
33. Aminophylline Paediatric tablets 100 mg
34. Aminophylline Suppositories 100 mg
35. Aminophylline Suppositories 150 mg

36. Aminophylline Suppositories 180 mg
37. Aminophylline Suppositories 360 mg
38. Aminophylline Suppositories 50 mg
39. Aminophylline Tablets 225 mg
40. Asmabec 100 Clickhaler (Focus Pharmaceuticals Ltd)
41. Asmabec 250 Clickhaler (Focus Pharmaceuticals Ltd)
42. Asmabec 50 Clickhaler (Focus Pharmaceuticals Ltd)
43. Asmabec Spacehaler 250 Inhaler with vortex generating actuator 250 micrograms/dose
44. Asmabec Spacehaler Inhaler with vortex generating actuator 100 micrograms/dose
45. Asmabec Spacehaler Inhaler with vortex generating actuator 50 micrograms/dose
46. Asmanex 200micrograms/dose Twisthaler (Organon Pharma (UK) Ltd)
47. Asmanex 400micrograms/dose Twisthaler (Organon Pharma (UK) Ltd)
48. Asmanex Twisthaler Dry Powder Inhaler 200 micrograms/dose, 30 doses
49. Asmanex Twisthaler Dry Powder Inhaler 200 micrograms/dose, 60 doses
50. Asmanex Twisthaler Dry Powder Inhaler 400 micrograms/dose, 30 doses
51. Asmanex Twisthaler Dry Powder Inhaler 400 micrograms/dose, 60 doses
52. Asmasal 95micrograms/dose Clickhaler (Focus Pharmaceuticals Ltd)
53. Asmasal Spacehaler Inhaler with vortex generating actuator 100 micrograms/dose
54. Asmaven Inhaler 100 micrograms/puff
55. Asmavent 100micrograms/dose inhaler CFC free (Kent Pharma (UK) Ltd)
56. Atimos Modulite 12micrograms/dose inhaler (Chiesi Ltd)
57. Atrovent 20micrograms/dose Autohaler (Boehringer Ingelheim Ltd)
58. Atrovent 20micrograms/dose inhaler (Boehringer Ingelheim Ltd)
59. Atrovent 20micrograms/dose inhaler CFC free (Boehringer Ingelheim Ltd)
60. Atrovent 250micrograms/1ml nebuliser liquid UDVs (Boehringer Ingelheim Ltd)
61. Atrovent 40microgram Aerocaps (Boehringer Ingelheim Ltd)
62. Atrovent 40microgram Aerocaps with Aerohaler (Boehringer Ingelheim Ltd)
63. Atrovent 500micrograms/2ml nebuliser liquid UDVs (Boehringer Ingelheim Ltd)
64. Atrovent Forte 40micrograms/dose inhaler (Boehringer Ingelheim Ltd)
65. Atrovent Nebules 500mcgs/2 ml
66. Atrovent Nebuliser solution 250 micrograms/ml
67. Bambec 10mg tablets (AstraZeneca UK Ltd)
68. Bambec 20mg tablets (AstraZeneca UK Ltd)
69. Bambuterol 10mg tablets
70. Bambuterol 20mg tablets
71. Bdp Spacehaler 100 micrograms/puff
72. Bdp Spacehaler 250 micrograms/puff
73. Bdp Spacehaler 50 micrograms/puff
74. Beclazone 100 Easi-Breathe inhaler (Teva UK Ltd)
75. Beclazone 100 inhaler (Teva UK Ltd)

76. Beclazone 200 inhaler (Teva UK Ltd)
77. Beclazone 250 Easi-Breathe inhaler (Teva UK Ltd)
78. Beclazone 250 inhaler (Teva UK Ltd)
79. Beclazone 50 Easi-Breathe inhaler (Teva UK Ltd)
80. Beclazone 50 inhaler (Teva UK Ltd)
81. Becloforte 250micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
82. Becloforte 400microgram disks (GlaxoSmithKline UK Ltd)
83. Becloforte 400microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
84. Becloforte Easi-Breathe Breath-actuated inhaler 250 micrograms/puff
85. Becloforte Integra Inhaler with spacer device 250 micrograms/puff
86. Becloforte Integra Refill 250 micrograms/puff
87. Becloforte Vm Inhalers and volumatic 250 micrograms/puff
88. Beclometasone 100 Cyclocaps (Teva UK Ltd)
89. Beclometasone 100microgram inhalation powder blisters
90. Beclometasone 100microgram inhalation powder blisters with device
91. Beclometasone 100microgram inhalation powder capsules
92. Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
93. Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free
94. Beclometasone 100micrograms/dose breath actuated inhaler
95. Beclometasone 100micrograms/dose breath actuated inhaler CFC free
96. Beclometasone 100micrograms/dose dry powder inhaler
97. Beclometasone 100micrograms/dose inhaler
98. Beclometasone 100micrograms/dose inhaler CFC free
99. Beclometasone 200 Cyclocaps (Teva UK Ltd)
100. Beclometasone 200microgram inhalation powder blisters
101. Beclometasone 200microgram inhalation powder blisters with device
102. Beclometasone 200microgram inhalation powder capsules
103. Beclometasone 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
104. Beclometasone 200micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free
105. Beclometasone 200micrograms/dose dry powder inhaler
106. Beclometasone 200micrograms/dose inhaler
107. Beclometasone 200micrograms/dose inhaler CFC free
108. Beclometasone 250micrograms/dose breath actuated inhaler
109. Beclometasone 250micrograms/dose dry powder inhaler
110. Beclometasone 250micrograms/dose inhaler
111. Beclometasone 250micrograms/dose inhaler CFC free
112. Beclometasone 400 Cyclocaps (Teva UK Ltd)
113. Beclometasone 400microgram inhalation powder blisters
114. Beclometasone 400microgram inhalation powder blisters with device
115. Beclometasone 400microgram inhalation powder capsules

116. Beclometasone 400micrograms/dose dry powder inhaler
117. Beclometasone 50micrograms/dose breath actuated inhaler
118. Beclometasone 50micrograms/dose breath actuated inhaler CFC free
119. Beclometasone 50micrograms/dose dry powder inhaler
120. Beclometasone 50micrograms/dose inhaler
121. Beclometasone 50micrograms/dose inhaler CFC free
122. Becodisks 100microgram (GlaxoSmithKline UK Ltd)
123. Becodisks 100microgram with Diskhaler (GlaxoSmithKline UK Ltd)
124. Becodisks 200microgram (GlaxoSmithKline UK Ltd)
125. Becodisks 200microgram with Diskhaler (GlaxoSmithKline UK Ltd)
126. Becodisks 400microgram (GlaxoSmithKline UK Ltd)
127. Becodisks 400microgram with Diskhaler (GlaxoSmithKline UK Ltd)
128. Becodisks Refill Powder 400 micrograms
129. Becodisks With Diskhaler Powder 400 micrograms
130. Becotide 100 Easi-Breathe Breath-actuated inhaler 100 micrograms/puff
131. Becotide 100 inhaler (GlaxoSmithKline UK Ltd)
132. Becotide 100microgram Rotacaps (GlaxoSmithKline UK Ltd)
133. Becotide 200 inhaler (GlaxoSmithKline UK Ltd)
134. Becotide 200microgram Rotacaps (GlaxoSmithKline UK Ltd)
135. Becotide 400microgram Rotacaps (GlaxoSmithKline UK Ltd)
136. Becotide 50 Easi-Breathe Breath-actuated inhaler 50 micrograms/puff
137. Becotide 50 inhaler (GlaxoSmithKline UK Ltd)
138. Becotide Rotahaler (GlaxoSmithKline UK Ltd)
139. Becotide Suspension 50 micrograms/ml
140. Berotec 200micrograms/dose inhaler (Boehringer Ingelheim Ltd)
141. Berotec Inhaler with extension 200 micrograms/puff
142. Biophylline Capsules 350 mg
143. Biophylline Capsules 500 mg
144. Biophylline Syrup 125 mg/5 ml
145. Bricanyl 1.5mg/5ml syrup (AstraZeneca UK Ltd)
146. Bricanyl 10mg/ml respirator solution (AstraZeneca UK Ltd)
147. Bricanyl 2.5mg/5ml solution for injection ampoules (AstraZeneca UK Ltd)
148. Bricanyl 250micrograms/dose inhaler (AstraZeneca UK Ltd)
149. Bricanyl 250micrograms/dose spacer inhaler (AstraZeneca UK Ltd)
150. Bricanyl 500micrograms/1ml solution for injection ampoules (AstraZeneca UK Ltd)
151. Bricanyl 500micrograms/dose Turbohaler (AstraZeneca UK Ltd)
152. Bricanyl 5mg tablets (AstraZeneca UK Ltd)
153. Bricanyl 5mg/2ml Respules (AstraZeneca UK Ltd)
154. Bricanyl Compound Tablets
155. Bricanyl Refill canister 250 micrograms/puff

156. Bricanyl Respirator solution 2.5 mg/ml
157. Bricanyl SA 7.5mg tablets (AstraZeneca UK Ltd)
158. Bricanyl Turbohaler Breath-Actuated Dry Powder Inhaler 500 micrograms/dose
159. Budelin Novolizer 200micrograms/dose inhalation powder (Mylan)
160. Budelin Novolizer 200micrograms/dose inhalation powder refill (Mylan)
161. Budesonide 100micrograms/dose / Formoterol 3micrograms/dose inhaler CFC free
162. Budesonide 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
163. Budesonide 100micrograms/dose dry powder inhaler
164. Budesonide 100micrograms/dose inhaler CFC free
165. Budesonide 1mg/2ml nebuliser liquid unit dose vials
166. Budesonide 200 Cyclocaps (Teva UK Ltd)
167. Budesonide 200microgram inhalation powder capsules
168. Budesonide 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
169. Budesonide 200micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free
170. Budesonide 200micrograms/dose dry powder inhalation cartridge
171. Budesonide 200micrograms/dose dry powder inhalation cartridge with device
172. Budesonide 200micrograms/dose dry powder inhaler
173. Budesonide 200micrograms/dose inhaler
174. Budesonide 200micrograms/dose inhaler CFC free
175. Budesonide 400 Cyclocaps (Teva UK Ltd)
176. Budesonide 400microgram inhalation powder capsules
177. Budesonide 400micrograms/dose / Formoterol 12micrograms/dose dry powder inhaler
178. Budesonide 400micrograms/dose dry powder inhaler
179. Budesonide 500micrograms/2ml nebuliser liquid unit dose vials
180. Budesonide 50micrograms/dose inhaler
181. Budesonide Breath-Actuated Dry Powder Inhaler 100 micrograms/dose
182. Budesonide Breath-Actuated Dry Powder Inhaler 200 micrograms/dose
183. Budesonide Inhaler with spacer device 200 micrograms/dose
184. Budesonide Refill canister 200 micrograms/dose
185. Budesonide Refill canister 50 micrograms/dose
186. Budesonide Spacer inhaler 200 micrograms/dose
187. Budesonide Spacer inhaler 50 micrograms/dose
188. Budesonide Turbohaler 100 micrograms/dose
189. Budesonide Turbohaler 400 micrograms/dose
190. CAM Mixture (Cambridge Healthcare Supplies Ltd)
191. Ciclesonide 160micrograms/dose inhaler CFC free
192. Ciclesonide 80micrograms/dose inhaler CFC free
193. Ciclesonide Cfc-free inhaler 160 micrograms/actuation, 120 doses
194. Ciclesonide Cfc-free inhaler 160 micrograms/actuation, 60 doses
195. Clenil Modulite 100micrograms/dose inhaler (Chiesi Ltd)

196. Clenil Modulite 200micrograms/dose inhaler (Chiesi Ltd)
197. Clenil Modulite 250micrograms/dose inhaler (Chiesi Ltd)
198. Clenil Modulite 50micrograms/dose inhaler (Chiesi Ltd)
199. Cobutolin Inhaler 100 micrograms
200. Cobutolin Tablets 2 mg
201. Cobutolin Tablets 4 mg
202. Combisal 25micrograms/dose / 125micrograms/dose inhaler (Aspire Pharma Ltd)
203. Combisal 25micrograms/dose / 250micrograms/dose inhaler (Aspire Pharma Ltd)
204. Combisal 25micrograms/dose / 50micrograms/dose inhaler (Aspire Pharma Ltd)
205. Combivent inhaler (Boehringer Ingelheim Ltd)
206. Combivent nebuliser liquid 2.5ml UDVs (Boehringer Ingelheim Ltd)
207. Combivent Nebuliser solution
208. Cromogen 20mg/2ml nebuliser liquid Steri-Neb unit dose vials (IVAX Pharmaceuticals UK Ltd)
209. Cromogen 5mg/dose Easi-Breathe inhaler (Teva UK Ltd)
210. Cromogen 5mg/dose inhaler (Teva UK Ltd)
211. Cromogen Nebules 20 mg/2 ml
212. Dilacort 2.5mg gastro-resistant tablets (Crescent Pharma Ltd)
213. Dilacort 5mg gastro-resistant tablets (Crescent Pharma Ltd)
214. DuoResp Spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (Teva UK Ltd)
215. DuoResp Spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (Teva UK Ltd)
216. Duovent Autohaler (Boehringer Ingelheim Ltd)
217. Duovent inhaler (Boehringer Ingelheim Ltd)
218. Duovent UDVs nebuliser liquid 4ml (Boehringer Ingelheim Ltd)
219. Easyhaler Beclometasone 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
220. Easyhaler Budesonide 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
221. Easyhaler Budesonide 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
222. Easyhaler Budesonide 400micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
223. Easyhaler Salbutamol sulfate 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
224. Easyhaler Salbutamol sulfate 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
225. Enerzair Breezhaler 114micrograms/dose / 46micrograms/dose / 136micrograms/dose inhalation powder capsules with device (Sandoz Ltd)
226. Ephedrine 15mg/5ml elixir
227. Ephedrine 30mg/10ml solution for injection ampoules
228. Ephedrine 30mg/10ml solution for injection pre-filled syringes
229. Ephedrine 30mg/1ml solution for injection ampoules
230. Ephedrine 4mg/5ml oral solution sugar free
231. Ephedrine hydrochloride 15mg tablets

232. Ephedrine hydrochloride 30mg tablets
233. Exirel Capsules 10 mg
234. Exirel Capsules 15 mg
235. Exirel Inhaler 200 micrograms/puff
236. Exirel Syrup 7.5 mg/5 ml
237. Fenoterol 1.25mg/4ml / Ipratropium 500micrograms/4ml nebuliser liquid unit dose vials
238. Fenoterol 100micrograms/dose / Ipratropium 40micrograms/dose inhaler
239. Fenoterol 200micrograms/dose inhaler
240. Fenoterol Hydrobromide Inhaler 100 micrograms/puff
241. Fenoterol Hydrobromide Solution 5 mg/ml
242. Fenoterol Hydrobromide With Extension Aerosol inhalation 200 micrograms/puff
243. Filair 100 inhaler (Meda Pharmaceuticals Ltd)
244. Filair 50 inhaler (Meda Pharmaceuticals Ltd)
245. Filair Forte 250micrograms/dose inhaler (Meda Pharmaceuticals Ltd)
246. Flixotide 0.5mg/2ml Nebules (GlaxoSmithKline UK Ltd)
247. Flixotide 100microgram disks (GlaxoSmithKline UK Ltd)
248. Flixotide 100microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
249. Flixotide 100micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
250. Flixotide 125micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
251. Flixotide 250microgram disks (GlaxoSmithKline UK Ltd)
252. Flixotide 250microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
253. Flixotide 250micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
254. Flixotide 250micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
255. Flixotide 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
256. Flixotide 2mg/2ml Nebules (GlaxoSmithKline UK Ltd)
257. Flixotide 500microgram disks (GlaxoSmithKline UK Ltd)
258. Flixotide 500microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
259. Flixotide 500micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
260. Flixotide 50microgram disks (GlaxoSmithKline UK Ltd)
261. Flixotide 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
262. Flixotide 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
263. Flixotide 50micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
264. Flixotide Inhaler 125 micrograms/puff
265. Flixotide Inhaler 250 micrograms/puff
266. Flixotide Inhaler 50 micrograms/puff
267. Fluticasone 125micrograms/dose / Formoterol 5micrograms/dose breath actuated inhaler CFC free
268. Fluticasone 125micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free
269. Fluticasone 125micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
270. Fluticasone 125micrograms/dose inhaler CFC free

271. Fluticasone 250micrograms/dose / Formoterol 10micrograms/dose inhaler CFC free
272. Fluticasone 250micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
273. Fluticasone 250micrograms/dose inhaler CFC free
274. Fluticasone 25micrograms/dose inhaler
275. Fluticasone 2mg/2ml nebuliser liquid unit dose vials
276. Fluticasone 500micrograms/2ml nebuliser liquid unit dose vials
277. Fluticasone 500micrograms/2ml nebuliser liquid unit dose vials (Imported)
278. Fluticasone 50micrograms/dose / Formoterol 5micrograms/dose breath actuated inhaler CFC free
279. Fluticasone 50micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free
280. Fluticasone 50micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
281. Fluticasone 50micrograms/dose inhaler CFC free
282. Fluticasone furoate 184micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler
283. Fluticasone furoate 92micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler
284. Fluticasone propionate 100microgram inhalation powder blisters
285. Fluticasone propionate 100microgram inhalation powder blisters with device
286. Fluticasone propionate 100micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler
287. Fluticasone propionate 100micrograms/dose dry powder inhaler
288. Fluticasone propionate 250microgram inhalation powder blisters
289. Fluticasone propionate 250microgram inhalation powder blisters with device
290. Fluticasone propionate 250micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler
291. Fluticasone propionate 250micrograms/dose dry powder inhaler
292. Fluticasone propionate 500microgram inhalation powder blisters
293. Fluticasone propionate 500microgram inhalation powder blisters with device
294. Fluticasone propionate 500micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler
295. Fluticasone propionate 500micrograms/dose dry powder inhaler
296. Fluticasone propionate 50microgram inhalation powder blisters
297. Fluticasone propionate 50microgram inhalation powder blisters with device
298. Fluticasone propionate 50micrograms/dose dry powder inhaler
299. Fluticasone Propionate Accuhaler 100 micrograms/dose
300. Fluticasone Propionate Accuhaler 250 micrograms/dose
301. Fluticasone Propionate Accuhaler 500 micrograms/dose
302. Fluticasone Propionate Disks with diskhaler 50 micrograms/dose
303. Fluticasone Propionate Disks with diskhaler 500 micrograms/puff
304. Fluticasone Propionate Inhaler 125 micrograms/puff
305. Fluticasone Propionate Inhaler 250 micrograms/puff
306. Fluticasone Propionate Inhaler 50 micrograms/puff
307. Flutiform 125micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)

308. Flutiform 250micrograms/dose / 10micrograms/dose inhaler (Napp Pharmaceuticals Ltd)
309. Flutiform 50micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)
310. Flutiform K-haler 125micrograms/dose / 5micrograms/dose breath actuated inhaler (Napp Pharmaceuticals Ltd)
311. Flutiform K-haler 50micrograms/dose / 5micrograms/dose breath actuated inhaler (Napp Pharmaceuticals Ltd)
312. Fobumix Easyhaler 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
313. Fobumix Easyhaler 320micrograms/dose / 9micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
314. Fobumix Easyhaler 80micrograms/dose / 4.5micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
315. Foradil 12microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
316. Formoterol 12microgram inhalation powder capsules with device
317. Formoterol 12micrograms/dose dry powder inhaler
318. Formoterol 12micrograms/dose inhaler CFC free
319. Formoterol 6micrograms/dose dry powder inhaler
320. Formoterol Dry Powder Inhaler 12 micrograms/actuation, 120 dose
321. Formoterol Dry Powder Inhaler 12 micrograms/actuation, 60 dose
322. Formoterol Easyhaler 12micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
323. Fostair 100micrograms/dose / 6micrograms/dose inhaler (Chiesi Ltd)
324. Fostair 200micrograms/dose / 6micrograms/dose inhaler (Chiesi Ltd)
325. Fostair NEXThaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (Chiesi Ltd)
326. Fostair NEXThaler 200micrograms/dose / 6micrograms/dose dry powder inhaler (Chiesi Ltd)
327. Franol Plus tablets (Sanofi)
328. Franol tablets (Sanofi)
329. Fusacomb Easyhaler 50micrograms/dose / 250micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
330. Fusacomb Easyhaler 50micrograms/dose / 500micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
331. Indacaterol 125micrograms/dose / Mometasone 127.5micrograms/dose inhalation powder capsules with device
332. Inhalvent 20micrograms/dose inhaler (Alissa Healthcare Research Ltd)
333. Intal 20mg Spincaps (Sanofi)
334. Intal 20mg/2ml nebuliser solution unit dose vials (Aventis Pharma)
335. Intal 5mg/dose Fisonair with spacer (Sanofi)
336. Intal 5mg/dose inhaler (Aventis Pharma)
337. Intal 5mg/dose inhaler CFC free (Sanofi)
338. Intal 5mg/dose Syncroner with spacer (Aventis Pharma)
339. Intal Autohaler 5 mg/metered dose
340. Intal Compound Spincaps
341. Ipramol nebuliser solution 2.5ml Steri-Neb unit dose vials (Teva UK Ltd)

342. Ipratropium 250micrograms/1ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
343. Ipratropium 250micrograms/1ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
344. Ipratropium 500micrograms/2ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
345. Ipratropium 500micrograms/2ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
346. Ipratropium bromide 20micrograms/dose breath actuated inhaler
347. Ipratropium bromide 20micrograms/dose inhaler
348. Ipratropium bromide 20micrograms/dose inhaler CFC free
349. Ipratropium bromide 250micrograms/1ml nebuliser liquid unit dose vials
350. Ipratropium bromide 40microgram inhalation powder capsules
351. Ipratropium bromide 40microgram inhalation powder capsules with device
352. Ipratropium bromide 40micrograms/dose inhaler
353. Ipratropium bromide 500micrograms/2ml nebuliser liquid unit dose vials
354. Ipratropium Bromide Nebuliser solution 250 micrograms/ml
355. Kelhale 100micrograms/dose inhaler (Cipla EU Ltd)
356. Kelhale 50micrograms/dose inhaler (Cipla EU Ltd)
357. Ketotifen 1mg capsules
358. Ketotifen 1mg tablets
359. Ketotifen 1mg/5ml oral solution sugar free
360. Ketotifen 1mg/5ml oral solution sugar free (Imported)
361. Ketotifen 1mg/5ml oral solution sugar free (Special Order)
362. Lasma Tablets 300 mg
363. Maxivent 2.5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
364. Maxivent 5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
365. Maxivent Inhaler 100 micrograms/puff
366. Mepolizumab 100mg powder for solution for injection vials
367. Mepolizumab 100mg/1ml solution for injection pre-filled disposable devices
368. Mepolizumab 100mg/1ml solution for injection pre-filled syringes
369. Montelukast 10mg tablets
370. Montelukast 4mg chewable tablets sugar free
371. Montelukast 4mg granules sachets sugar free
372. Montelukast 5mg chewable tablets sugar free
373. Nedocromil 2mg/dose inhaler
374. Nedocromil 2mg/dose inhaler CFC free
375. Nedocromil 2mg/dose inhaler with spacer
376. Neovent 25micrograms/dose inhaler CFC free (Kent Pharma (UK) Ltd)
377. Norphyllin SR 225mg tablets (Teva UK Ltd)
378. Novolizer Budesonide Inhalation Cartridge + Device 200 micrograms/dose, 100 doses
379. Novolizer Budesonide Inhalation Cartridge Refill 200 micrograms/dose, 100 doses
380. Novolizer Salbulin Inhalation Cartridge + Device 100 micrograms/dose

381. Novolizer Salbulin Inhalation Cartridge Refill 100 micrograms/dose
382. Nucala 100mg powder for solution for injection vials (GlaxoSmithKline UK Ltd)
383. Nucala 100mg/1ml solution for injection pre-filled pens (GlaxoSmithKline UK Ltd)
384. Nuelin 125mg tablets (3M Health Care Ltd)
385. Nuelin 60mg/5ml liquid (3M Health Care Ltd)
386. Nuelin SA 175mg tablets (Mylan)
387. Nuelin SA 250 tablets (Mylan)
388. Omalizumab 150mg powder and solvent for solution for injection vials
389. Omalizumab 150mg/1ml solution for injection pre-filled syringes
390. Omalizumab 75mg/0.5ml solution for injection pre-filled syringes
391. Onbrez Breezhaler 150microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
392. Onbrez Breezhaler 300microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
393. Orciprenaline 10mg/5ml oral solution sugar free
394. Orciprenaline 20mg tablets
395. Orciprenaline Sulfate Aerosol 0.75 mg
396. Orciprenaline Sulfate Refill 750 micrograms/dose
397. Oxis 12 Turbohaler (AstraZeneca UK Ltd)
398. Oxis 6 Turbohaler (AstraZeneca UK Ltd)
399. Phyllocontin Continus 225mg tablets (Napp Pharmaceuticals Ltd)
400. Phyllocontin Forte Continus 350mg tablets (Napp Pharmaceuticals Ltd)
401. Phyllocontin Paediatric Continus 100mg tablets (Napp Pharmaceuticals Ltd)
402. Pirbuterol Capsules 10 mg
403. Pirbuterol Capsules 15 mg
404. Pirbuterol Inhaler 200 micrograms/puff
405. Pirbuterol Syrup 7.5 mg/5 ml
406. Prednisolone 10mg tablets
407. Prednisolone 10mg/ml oral solution sugar free
408. Prednisolone 15mg/5ml oral solution
409. Prednisolone 1mg tablets
410. Prednisolone 2.5mg tablets
411. Prednisolone 20mg tablets
412. Prednisolone 25mg tablets
413. Prednisolone 30mg tablets
414. Prednisolone 5mg soluble tablets
415. Prednisolone 5mg tablets
416. Prednisolone 5mg/5ml oral solution unit dose
417. Pro-Vent Capsules 300 mg
418. Pulmicort 0.5mg Respules (AstraZeneca UK Ltd)
419. Pulmicort 100 Turbohaler (AstraZeneca UK Ltd)

420. Pulmicort 100micrograms/dose inhaler CFC free (AstraZeneca UK Ltd)
421. Pulmicort 1mg Respules (AstraZeneca UK Ltd)
422. Pulmicort 200 Turbohaler (AstraZeneca UK Ltd)
423. Pulmicort 200micrograms/dose inhaler (AstraZeneca UK Ltd)
424. Pulmicort 200micrograms/dose inhaler CFC free (AstraZeneca UK Ltd)
425. Pulmicort 200micrograms/dose inhaler with Nebuchamber (AstraZeneca UK Ltd)
426. Pulmicort 400 Turbohaler (AstraZeneca UK Ltd)
427. Pulmicort LS 50micrograms/dose inhaler (AstraZeneca UK Ltd)
428. Pulmicort Ls Refill canister 50 micrograms/dose
429. Pulmicort Refill canister 200 micrograms/dose
430. Pulmicort Spacer inhaler 200 micrograms/dose
431. Pulmicort Spacer inhaler 50 micrograms/dose
432. Pulmicort Turbohaler Breath-Actuated Dry Powder Inhaler 100 micrograms/dose
433. Pulmicort Turbohaler Breath-Actuated Dry Powder Inhaler 200 micrograms/dose
434. Pulmicort Turbohaler Breath-Actuated Dry Powder Inhaler 400 micrograms/dose
435. Pulvinal Beclometasone Dipropionate 100micrograms/dose dry powder inhaler (Chiesi Ltd)
436. Pulvinal Beclometasone Dipropionate 200micrograms/dose dry powder inhaler (Chiesi Ltd)
437. Pulvinal Beclometasone Dipropionate 400micrograms/dose dry powder inhaler (Chiesi Ltd)
438. Pulvinal Salbutamol 200micrograms/dose dry powder inhaler (Chiesi Ltd)
439. Qvar 100 Autohaler (Teva UK Ltd)
440. Qvar 100 inhaler (Teva UK Ltd)
441. Qvar 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
442. Qvar 50 Autohaler (Teva UK Ltd)
443. Qvar 50 inhaler (Teva UK Ltd)
444. Qvar 50micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
445. Relvar Ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)
446. Relvar Ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)
447. Respontin 250micrograms/1ml Nebules (GlaxoSmithKline UK Ltd)
448. Respontin 500micrograms/2ml Nebules (GlaxoSmithKline UK Ltd)
449. Salamol 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
450. Salamol 100micrograms/dose inhaler CFC free (Teva UK Ltd)
451. Salamol 2.5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
452. Salamol 5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
453. Salamol Easi-Breathe Breath-actuated inhaler 100 micrograms/puff
454. Salamol Inhaler 100 micrograms/puff
455. Salamol Nebuliser solution 2.5 mg/2.5 ml
456. Salapin 2mg/5ml syrup (Pinewood Healthcare)
457. Salbulin 100micrograms/dose inhaler (3M Health Care Ltd)
458. Salbulin Cfc-free inhaler 100 micrograms/puff

459. Salbulin Liquid 2 mg/5 ml
460. Salbulin Novolizer 100micrograms/dose inhalation powder (Mylan)
461. Salbulin Novolizer 100micrograms/dose inhalation powder refill (Mylan)
462. Salbulin Tablets 2 mg
463. Salbulin Tablets 4 mg
464. Salbutamol 100micrograms/dose / Ipratropium 20micrograms/dose inhaler
465. Salbutamol 100micrograms/dose breath actuated inhaler
466. Salbutamol 100micrograms/dose breath actuated inhaler CFC free
467. Salbutamol 100micrograms/dose dry powder inhalation cartridge
468. Salbutamol 100micrograms/dose dry powder inhalation cartridge with device
469. Salbutamol 100micrograms/dose dry powder inhaler
470. Salbutamol 100micrograms/dose inhaler
471. Salbutamol 100micrograms/dose inhaler CFC free
472. Salbutamol 2.5mg/2.5ml / Ipratropium bromide 500micrograms/2.5ml nebuliser liquid ampoules
473. Salbutamol 2.5mg/2.5ml / Ipratropium bromide 500micrograms/2.5ml nebuliser liquid unit dose vials
474. Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
475. Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials
476. Salbutamol 200 Cyclocaps (Teva UK Ltd)
477. Salbutamol 200microgram inhalation powder blisters
478. Salbutamol 200microgram inhalation powder blisters with device
479. Salbutamol 200microgram inhalation powder capsules
480. Salbutamol 200micrograms/dose dry powder inhaler
481. Salbutamol 2mg tablets
482. Salbutamol 2mg/5ml oral solution sugar free
483. Salbutamol 400 Cyclocaps (Teva UK Ltd)
484. Salbutamol 400microgram inhalation powder blisters
485. Salbutamol 400microgram inhalation powder blisters with device
486. Salbutamol 400microgram inhalation powder capsules
487. Salbutamol 4mg modified-release capsules
488. Salbutamol 4mg modified-release tablets
489. Salbutamol 4mg tablets
490. Salbutamol 500micrograms/1ml solution for injection ampoules
491. Salbutamol 5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
492. Salbutamol 5mg/2.5ml nebuliser liquid unit dose vials
493. Salbutamol 5mg/5ml solution for infusion ampoules
494. Salbutamol 5mg/ml nebuliser liquid
495. Salbutamol 8mg modified-release capsules
496. Salbutamol 8mg modified-release tablets
497. Salbutamol 95micrograms/dose dry powder inhaler

498. Salbutamol Accuhaler 200 micrograms/dose
499. Salbutamol Aerosol inhalation 100 micrograms/metered inhalation
500. Salbutamol Autohaler 100 micrograms/puff
501. Salbutamol Breath Actuated Pressurised Inhalation 100 micrograms/actuation
502. Salbutamol Breath Actuated Pressurised Inhalation, Cfc-free 100 micrograms/actuation
503. Salbutamol Cyclocaps 200 micrograms
504. Salbutamol Cyclocaps 400 micrograms
505. Salbutamol Dry powder disks + disk inhaler 200 micrograms
506. Salbutamol Dry powder disks + disk inhaler 400 micrograms
507. Salbutamol Dry powder for inhalation 400 micrograms/dose
508. Salbutamol Dry Powder Inhaler 200 micrograms/actuation, 200 dose
509. Salbutamol Inhaler with vortex generating actuator 100 micrograms/dose
510. Salbutamol Injection 50 micrograms/ml
511. Salbutamol Nebules 0.1 %
512. Salbutamol Rotacaps 200 micrograms
513. Salbutamol Rotacaps 400 micrograms
514. Salbutamol Rotahaler 1
515. Salbutamol Spacehaler 100 micrograms/puff
516. Salbutamol Spandets 8 mg
517. Salbutamol Sr Spandet(s) 8 mg
518. Salbutamol Syrup 1 mg/5 ml
519. Salbuvent Aerosol inhalation 100mcg/inhalation
520. Salbuvent Injection 500mcg/ml
521. Salbuvent Injection 50mcg/ml
522. Salbuvent Respirator solution 5mg/ml
523. Salbuvent Solution for intravenous infusion 1mg/ml
524. Salbuvent Syrup 2mg/5 ml
525. Salbuvent Tablets 2 mg
526. Salbuvent Tablets 4 mg
527. Salipraneb 0.5mg/2.5mg nebuliser solution 2.5ml ampoules (Actavis UK Ltd)
528. Salmeterol 25micrograms/dose inhaler
529. Salmeterol 25micrograms/dose inhaler CFC free
530. Salmeterol 50microgram inhalation powder blisters
531. Salmeterol 50microgram inhalation powder blisters with device
532. Salmeterol 50micrograms/dose dry powder inhaler
533. Salmeterol Xinafoate Disks with diskhaler 50 micrograms/blister
534. Seebri Breezhaler 44microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
535. Sereflo 25micrograms/dose / 125micrograms/dose inhaler (Cipla EU Ltd)
536. Sereflo 25micrograms/dose / 250micrograms/dose inhaler (Cipla EU Ltd)

537. Seretide 100 Accuhaler (GlaxoSmithKline UK Ltd)
538. Seretide 125 Evohaler (GlaxoSmithKline UK Ltd)
539. Seretide 250 Accuhaler (GlaxoSmithKline UK Ltd)
540. Seretide 250 Evohaler (GlaxoSmithKline UK Ltd)
541. Seretide 50 Evohaler (GlaxoSmithKline UK Ltd)
542. Seretide 500 Accuhaler (GlaxoSmithKline UK Ltd)
543. Serevent 25micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
544. Serevent 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
545. Serevent 50microgram disks (GlaxoSmithKline UK Ltd)
546. Serevent 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
547. Serevent 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
548. Singulair 10mg tablets (Organon Pharma (UK) Ltd)
549. Singulair Paediatric 4mg chewable tablets (Organon Pharma (UK) Ltd)
550. Singulair Paediatric 4mg granules sachets (Organon Pharma (UK) Ltd)
551. Singulair Paediatric 5mg chewable tablets (Organon Pharma (UK) Ltd)
552. Sirdupla 25micrograms/dose / 125micrograms/dose inhaler (Mylan)
553. Sirdupla 25micrograms/dose / 250micrograms/dose inhaler (Mylan)
554. Slo-Phyllin 125mg capsules (Merck Serono Ltd)
555. Slo-Phyllin 250mg capsules (Merck Serono Ltd)
556. Slo-Phyllin 60mg capsules (Merck Serono Ltd)
557. Sodium cromoglicate 20mg inhalation powder capsules
558. Sodium cromoglicate 20mg/2ml nebuliser liquid unit dose vials
559. Sodium cromoglicate 5mg/dose breath actuated inhaler
560. Sodium cromoglicate 5mg/dose inhaler
561. Sodium cromoglicate 5mg/dose inhaler CFC free
562. Sodium cromoglicate 5mg/dose inhaler with spacer
563. Sodium Cromoglicate Inhaler With Integral Spacer Device 5 mg/actuation
564. Soltel 25micrograms/dose inhaler CFC free (Cipla EU Ltd)
565. Soprobec 100micrograms/dose inhaler (Glenmark Pharmaceuticals Europe Ltd)
566. Soprobec 200micrograms/dose inhaler (Glenmark Pharmaceuticals Europe Ltd)
567. Soprobec 250micrograms/dose inhaler (Glenmark Pharmaceuticals Europe Ltd)
568. Soprobec 50micrograms/dose inhaler (Glenmark Pharmaceuticals Europe Ltd)
569. Spiriva Respimat 2.5micrograms/dose inhalation solution cartridge with device (Boehringer Ingelheim Ltd)
570. Spiriva Respimat 2.5micrograms/dose inhalation solution refill cartridge (Boehringer Ingelheim Ltd)
571. Stalpex 50micrograms/dose / 500micrograms/dose dry powder inhaler (Glenmark Pharmaceuticals Europe Ltd)
572. Symbicort 100/6 Turbohaler (AstraZeneca UK Ltd)
573. Symbicort 100micrograms/dose / 3micrograms/dose pressurised inhaler (AstraZeneca UK Ltd)
574. Symbicort 200/6 Turbohaler (AstraZeneca UK Ltd)

575. Symbicort 200micrograms/dose / 6micrograms/dose pressurised inhaler (AstraZeneca UK Ltd)
576. Symbicort 400/12 Turbohaler (AstraZeneca UK Ltd)
577. Tedral Tablets
578. Terbutaline 1.5mg/5ml oral solution sugar free
579. Terbutaline 10mg/ml nebuliser liquid
580. Terbutaline 2.5mg/5ml solution for injection ampoules
581. Terbutaline 250micrograms/dose inhaler
582. Terbutaline 250micrograms/dose inhaler with spacer
583. Terbutaline 500micrograms/1ml solution for injection ampoules
584. Terbutaline 500micrograms/dose dry powder inhaler
585. Terbutaline 5mg tablets
586. Terbutaline 5mg/2ml nebuliser liquid unit dose vials
587. Terbutaline 7.5mg modified-release tablets
588. Terbutaline Nebulisation single dose unit 5 mg/2 ml
589. Terbutaline Sulfate Refill canister 250 micrograms/puff
590. Terbutaline Sulfate Respirator solution 2.5 mg/ml
591. Theo-Dur 200mg tablets (AstraZeneca UK Ltd)
592. Theo-Dur 300mg tablets (AstraZeneca UK Ltd)
593. Theograd Tablets 350 mg
594. Theophylline 125mg modified-release capsules
595. Theophylline 125mg tablets
596. Theophylline 175mg modified-release tablets
597. Theophylline 200mg modified-release tablets
598. Theophylline 250mg modified-release capsules
599. Theophylline 250mg modified-release tablets
600. Theophylline 300mg modified-release tablets
601. Theophylline 400mg modified-release tablets
602. Theophylline 50mg/5ml oral solution
603. Theophylline 50mg/5ml oral suspension
604. Theophylline 60mg modified-release capsules
605. Theophylline 60mg/5ml oral solution
606. Theophylline Capsules 300 mg
607. Theophylline Hydrate Syrup 125 mg/5 ml
608. Theophylline Paediatric tablets 200 mg
609. Theophylline S/R Capsules 300 mg
610. Theophylline S/R Tablets 500 mg
611. Theophylline Tablets 120 mg
612. Theophylline Tablets 200 mg
613. Theophylline Tablets 250 mg
614. Theophylline Tablets 300 mg

615. Theophylline Tablets 350 mg
616. Theophylline Tablets 400 mg
617. Tilade 2mg/dose inhaler (Sanofi)
618. Tilade 2mg/dose inhaler CFC free (Sanofi)
619. Tilade 2mg/dose Syncroner with spacer (Sanofi)
620. Tiotropium bromide 2.5micrograms/dose / Olodaterol 2.5micrograms/dose inhalation solution cartridge CFC free
621. Tiotropium bromide 2.5micrograms/dose inhalation solution cartridge CFC free
622. Tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device CFC free
623. Tropiovent 250micrograms/1ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
624. Tropiovent 500micrograms/2ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
625. Ultibro Breezhaler 85microgram/43microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
626. Uniphyllin Continus 200mg tablets (Napp Pharmaceuticals Ltd)
627. Uniphyllin Continus 300mg tablets (Napp Pharmaceuticals Ltd)
628. Uniphyllin Continus 400mg tablets (Napp Pharmaceuticals Ltd)
629. Ventide inhaler (GlaxoSmithKline UK Ltd)
630. Ventide Paediatric Rotacaps (GlaxoSmithKline UK Ltd)
631. Ventide Rotacaps (GlaxoSmithKline UK Ltd)
632. Ventide Rotahaler (GlaxoSmithKline UK Ltd)
633. Ventmax SR 4mg capsules (Chiesi Ltd)
634. Ventmax SR 8mg capsules (Chiesi Ltd)
635. Ventodisks 200microgram (GlaxoSmithKline UK Ltd)
636. Ventodisks 200microgram with Diskhaler (GlaxoSmithKline UK Ltd)
637. Ventodisks 400microgram (GlaxoSmithKline UK Ltd)
638. Ventodisks 400microgram with Diskhaler (GlaxoSmithKline UK Ltd)
639. Ventolin 100micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
640. Ventolin 2.5mg Nebules (GlaxoSmithKline UK Ltd)
641. Ventolin 200microgram Rotacaps (GlaxoSmithKline UK Ltd)
642. Ventolin 200micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
643. Ventolin 2mg/5ml syrup (GlaxoSmithKline UK Ltd)
644. Ventolin 400microgram Rotacaps (GlaxoSmithKline UK Ltd)
645. Ventolin 500micrograms/1ml solution for injection ampoules (GlaxoSmithKline UK Ltd)
646. Ventolin 5mg Nebules (GlaxoSmithKline UK Ltd)
647. Ventolin 5mg/5ml solution for infusion ampoules (GlaxoSmithKline UK Ltd)
648. Ventolin 5mg/ml respirator solution (GlaxoSmithKline UK Ltd)
649. Ventolin Cr S/r tablets 4 mg
650. Ventolin Cr S/r tablets 8 mg
651. Ventolin Easi-Breathe Breath-actuated inhaler 100 micrograms/puff

652. Ventolin Inhaler 100 micrograms/puff
653. Ventolin Injection 50 micrograms/ml
654. Ventolin Rotahaler (GlaxoSmithKline UK Ltd)
655. Ventolin Spandets 8 mg
656. Ventolin Tablets 2 mg
657. Ventolin Tablets 4 mg
658. Vertine 25micrograms/dose inhaler CFC free (Teva UK Ltd)
659. Volmax 4mg modified-release tablets (GlaxoSmithKline UK Ltd)
660. Volmax 8mg modified-release tablets (GlaxoSmithKline UK Ltd)
661. Xolair 150mg powder and solvent for solution for injection vials (Novartis Pharmaceuticals UK Ltd)
662. Xolair 150mg/1ml solution for injection pre-filled syringes (Novartis Pharmaceuticals UK Ltd)
663. Xolair 75mg/0.5ml solution for injection pre-filled syringes (Novartis Pharmaceuticals UK Ltd)
664. Zaditen 1mg capsules (Novartis Pharmaceuticals UK Ltd)
665. Zaditen 1mg tablets (CD Pharma Srl)
666. Zaditen 1mg/5ml elixir (CD Pharma Srl)
667. Zafirlukast 20mg tablets

Appendix G: Asthma preventers medication for school-age children with asthma.

TermfromEMIS

1. Accolate 20mg tablets (AstraZeneca UK Ltd)
2. Aerivio Spiromax 50micrograms/dose / 500micrograms/dose dry powder inhaler (Teva UK Ltd)
3. AeroBec 100 Autohaler (Meda Pharmaceuticals Ltd)
4. AeroBec 50 Autohaler (Meda Pharmaceuticals Ltd)
5. AeroBec Forte 250 Autohaler (Meda Pharmaceuticals Ltd)
6. Aerocrom inhaler (Castlemead Healthcare Ltd)
7. Aerocrom Syncroner with spacer (Castlemead Healthcare Ltd)
8. AirFluSal 25micrograms/dose / 125micrograms/dose inhaler (Sandoz Ltd)
9. AirFluSal 25micrograms/dose / 250micrograms/dose inhaler (Sandoz Ltd)
10. AirFluSal Forspiro 50micrograms/dose / 500micrograms/dose dry powder inhaler (Sandoz Ltd)
11. Aloflute 25micrograms/dose / 125micrograms/dose inhaler (Mylan)
12. Aloflute 25micrograms/dose / 250micrograms/dose inhaler (Mylan)
13. Alvesco 160 inhaler (AstraZeneca UK Ltd)
14. Alvesco 80 inhaler (AstraZeneca UK Ltd)
15. Alvesco Cfc-free inhaler 160 micrograms/actuation, 120 doses
16. Alvesco Cfc-free inhaler 160 micrograms/actuation, 60 doses
17. Aminophylline 100mg tablets
18. Aminophylline 225mg modified-release tablets
19. Aminophylline hydrate 225mg modified-release tablets
20. Aminophylline hydrate 350mg modified-release tablets
21. Aminophylline Paediatric tablets 100 mg
22. Aminophylline Tablets 225 mg
23. Asmabec 100 Clickhaler (Focus Pharmaceuticals Ltd)
24. Asmabec 250 Clickhaler (Focus Pharmaceuticals Ltd)
25. Asmabec 50 Clickhaler (Focus Pharmaceuticals Ltd)
26. Asmabec Spacehaler 250 Inhaler with vortex generating actuator 250 micrograms/dose
27. Asmabec Spacehaler Inhaler with vortex generating actuator 100 micrograms/dose
28. Asmabec Spacehaler Inhaler with vortex generating actuator 50 micrograms/dose
29. Asmanex 200micrograms/dose Twisthaler (Organon Pharma (UK) Ltd)
30. Asmanex 400micrograms/dose Twisthaler (Organon Pharma (UK) Ltd)
31. Asmanex Twisthaler Dry Powder Inhaler 200 micrograms/dose, 30 doses
32. Asmanex Twisthaler Dry Powder Inhaler 200 micrograms/dose, 60 doses
33. Asmanex Twisthaler Dry Powder Inhaler 400 micrograms/dose, 30 doses
34. Asmanex Twisthaler Dry Powder Inhaler 400 micrograms/dose, 60 doses
35. Atimos Modulite 12micrograms/dose inhaler (Chiesi Ltd)
36. Bambec 10mg tablets (AstraZeneca UK Ltd)

37. Bambec 20mg tablets (AstraZeneca UK Ltd)
38. Bambuterol 10mg tablets
39. Bambuterol 20mg tablets
40. Bdp Spacehaler 100 micrograms/puff
41. Bdp Spacehaler 250 micrograms/puff
42. Bdp Spacehaler 50 micrograms/puff
43. Beclazone 100 Easi-Breathe inhaler (Teva UK Ltd)
44. Beclazone 100 inhaler (Teva UK Ltd)
45. Beclazone 200 inhaler (Teva UK Ltd)
46. Beclazone 250 Easi-Breathe inhaler (Teva UK Ltd)
47. Beclazone 250 inhaler (Teva UK Ltd)
48. Beclazone 50 Easi-Breathe inhaler (Teva UK Ltd)
49. Beclazone 50 inhaler (Teva UK Ltd)
50. Becloforte 250micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
51. Becloforte 400microgram disks (GlaxoSmithKline UK Ltd)
52. Becloforte 400microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
53. Becloforte Easi-Breathe Breath-actuated inhaler 250 micrograms/puff
54. Becloforte Integra Inhaler with spacer device 250 micrograms/puff
55. Becloforte Integra Refill 250 micrograms/puff
56. Becloforte Vm Inhalers and volumatic 250 micrograms/puff
57. Beclometasone 100 Cyclocaps (Teva UK Ltd)
58. Beclometasone 100microgram inhalation powder blisters
59. Beclometasone 100microgram inhalation powder blisters with device
60. Beclometasone 100microgram inhalation powder capsules
61. Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
62. Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free
63. Beclometasone 100micrograms/dose breath actuated inhaler
64. Beclometasone 100micrograms/dose breath actuated inhaler CFC free
65. Beclometasone 100micrograms/dose dry powder inhaler
66. Beclometasone 100micrograms/dose inhaler
67. Beclometasone 100micrograms/dose inhaler CFC free
68. Beclometasone 200 Cyclocaps (Teva UK Ltd)
69. Beclometasone 200microgram inhalation powder blisters
70. Beclometasone 200microgram inhalation powder blisters with device
71. Beclometasone 200microgram inhalation powder capsules
72. Beclometasone 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
73. Beclometasone 200micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free
74. Beclometasone 200micrograms/dose dry powder inhaler
75. Beclometasone 200micrograms/dose inhaler
76. Beclometasone 200micrograms/dose inhaler CFC free
77. Beclometasone 250micrograms/dose breath actuated inhaler

78. Beclometasone 250micrograms/dose dry powder inhaler
79. Beclometasone 250micrograms/dose inhaler
80. Beclometasone 250micrograms/dose inhaler CFC free
81. Beclometasone 400 Cyclocaps (Teva UK Ltd)
82. Beclometasone 400microgram inhalation powder blisters
83. Beclometasone 400microgram inhalation powder blisters with device
84. Beclometasone 400microgram inhalation powder capsules
85. Beclometasone 400micrograms/dose dry powder inhaler
86. Beclometasone 50micrograms/dose breath actuated inhaler
87. Beclometasone 50micrograms/dose breath actuated inhaler CFC free
88. Beclometasone 50micrograms/dose dry powder inhaler
89. Beclometasone 50micrograms/dose inhaler
90. Beclometasone 50micrograms/dose inhaler CFC free
91. Becodisks 100microgram (GlaxoSmithKline UK Ltd)
92. Becodisks 100microgram with Diskhaler (GlaxoSmithKline UK Ltd)
93. Becodisks 200microgram (GlaxoSmithKline UK Ltd)
94. Becodisks 200microgram with Diskhaler (GlaxoSmithKline UK Ltd)
95. Becodisks 400microgram (GlaxoSmithKline UK Ltd)
96. Becodisks 400microgram with Diskhaler (GlaxoSmithKline UK Ltd)
97. Becodisks Refill Powder 400 micrograms
98. Becodisks With Diskhaler Powder 400 micrograms
99. Becotide 100 Easi-Breathe Breath-actuated inhaler 100 micrograms/puff
100. Becotide 100 inhaler (GlaxoSmithKline UK Ltd)
101. Becotide 100microgram Rotacaps (GlaxoSmithKline UK Ltd)
102. Becotide 200 inhaler (GlaxoSmithKline UK Ltd)
103. Becotide 200microgram Rotacaps (GlaxoSmithKline UK Ltd)
104. Becotide 400microgram Rotacaps (GlaxoSmithKline UK Ltd)
105. Becotide 50 Easi-Breathe Breath-actuated inhaler 50 micrograms/puff
106. Becotide 50 inhaler (GlaxoSmithKline UK Ltd)
107. Becotide Rotahaler (GlaxoSmithKline UK Ltd)
108. Becotide Suspension 50 micrograms/ml
109. Budelin Novolizer 200micrograms/dose inhalation powder (Mylan)
110. Budelin Novolizer 200micrograms/dose inhalation powder refill (Mylan)
111. Budesonide 100micrograms/dose / Formoterol 3micrograms/dose inhaler CFC free
112. Budesonide 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
113. Budesonide 100micrograms/dose dry powder inhaler
114. Budesonide 100micrograms/dose inhaler CFC free
115. Budesonide 1mg/2ml nebuliser liquid unit dose vials
116. Budesonide 200 Cyclocaps (Teva UK Ltd)
117. Budesonide 200microgram inhalation powder capsules
118. Budesonide 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler

119. Budesonide 200micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free
120. Budesonide 200micrograms/dose dry powder inhalation cartridge
121. Budesonide 200micrograms/dose dry powder inhalation cartridge with device
122. Budesonide 200micrograms/dose dry powder inhaler
123. Budesonide 200micrograms/dose inhaler
124. Budesonide 200micrograms/dose inhaler CFC free
125. Budesonide 400 Cyclocaps (Teva UK Ltd)
126. Budesonide 400microgram inhalation powder capsules
127. Budesonide 400micrograms/dose / Formoterol 12micrograms/dose dry powder inhaler
128. Budesonide 400micrograms/dose dry powder inhaler
129. Budesonide 500micrograms/2ml nebuliser liquid unit dose vials
130. Budesonide 50micrograms/dose inhaler
131. Budesonide Breath-Actuated Dry Powder Inhaler 100 micrograms/dose
132. Budesonide Breath-Actuated Dry Powder Inhaler 200 micrograms/dose
133. Budesonide Inhaler with spacer device 200 micrograms/dose
134. Budesonide Refill canister 200 micrograms/dose
135. Budesonide Refill canister 50 micrograms/dose
136. Budesonide Spacer inhaler 200 micrograms/dose
137. Budesonide Spacer inhaler 50 micrograms/dose
138. Budesonide Turbohaler 100 micrograms/dose
139. Budesonide Turbohaler 400 micrograms/dose
140. Ciclesonide 160micrograms/dose inhaler CFC free
141. Ciclesonide 80micrograms/dose inhaler CFC free
142. Ciclesonide Cfc-free inhaler 160 micrograms/actuation, 120 doses
143. Ciclesonide Cfc-free inhaler 160 micrograms/actuation, 60 doses
144. Clenil Modulite 100micrograms/dose inhaler (Chiesi Ltd)
145. Clenil Modulite 200micrograms/dose inhaler (Chiesi Ltd)
146. Clenil Modulite 250micrograms/dose inhaler (Chiesi Ltd)
147. Clenil Modulite 50micrograms/dose inhaler (Chiesi Ltd)
148. Combisal 25micrograms/dose / 125micrograms/dose inhaler (Aspire Pharma Ltd)
149. Combisal 25micrograms/dose / 250micrograms/dose inhaler (Aspire Pharma Ltd)
150. Combisal 25micrograms/dose / 50micrograms/dose inhaler (Aspire Pharma Ltd)
151. Cromogen 20mg/2ml nebuliser liquid Steri-Neb unit dose vials (IVAX Pharmaceuticals UK Ltd)
152. Cromogen 5mg/dose Easi-Breathe inhaler (Teva UK Ltd)
153. Cromogen 5mg/dose inhaler (Teva UK Ltd)
154. Cromogen Nebules 20 mg/2 ml
155. Dilacort 2.5mg gastro-resistant tablets (Crescent Pharma Ltd)
156. Dilacort 5mg gastro-resistant tablets (Crescent Pharma Ltd)
157. DuoResp Spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (Teva UK Ltd)

158. DuoResp Spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (Teva UK Ltd)
159. Easyhaler Beclometasone 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
160. Easyhaler Budesonide 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
161. Easyhaler Budesonide 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
162. Easyhaler Budesonide 400micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
163. Enerzair Breezhaler 114micrograms/dose / 46micrograms/dose / 136micrograms/dose inhalation powder capsules with device (Sandoz Ltd)
164. Filair 100 inhaler (Meda Pharmaceuticals Ltd)
165. Filair 50 inhaler (Meda Pharmaceuticals Ltd)
166. Filair Forte 250micrograms/dose inhaler (Meda Pharmaceuticals Ltd)
167. Flixotide 0.5mg/2ml Nebules (GlaxoSmithKline UK Ltd)
168. Flixotide 100microgram disks (GlaxoSmithKline UK Ltd)
169. Flixotide 100microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
170. Flixotide 100micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
171. Flixotide 125micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
172. Flixotide 250microgram disks (GlaxoSmithKline UK Ltd)
173. Flixotide 250microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
174. Flixotide 250micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
175. Flixotide 250micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
176. Flixotide 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
177. Flixotide 2mg/2ml Nebules (GlaxoSmithKline UK Ltd)
178. Flixotide 500microgram disks (GlaxoSmithKline UK Ltd)
179. Flixotide 500microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
180. Flixotide 500micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
181. Flixotide 50microgram disks (GlaxoSmithKline UK Ltd)
182. Flixotide 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
183. Flixotide 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
184. Flixotide 50micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
185. Flixotide Inhaler 125 micrograms/puff
186. Flixotide Inhaler 250 micrograms/puff
187. Flixotide Inhaler 50 micrograms/puff
188. Fluticasone 125micrograms/dose / Formoterol 5micrograms/dose breath actuated inhaler CFC free
189. Fluticasone 125micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free
190. Fluticasone 125micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
191. Fluticasone 125micrograms/dose inhaler CFC free
192. Fluticasone 250micrograms/dose / Formoterol 10micrograms/dose inhaler CFC free
193. Fluticasone 250micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
194. Fluticasone 250micrograms/dose inhaler CFC free
195. Fluticasone 25micrograms/dose inhaler

196. Fluticasone 2mg/2ml nebuliser liquid unit dose vials
197. Fluticasone 500micrograms/2ml nebuliser liquid unit dose vials
198. Fluticasone 500micrograms/2ml nebuliser liquid unit dose vials (Imported)
199. Fluticasone 50micrograms/dose / Formoterol 5micrograms/dose breath actuated inhaler CFC free
200. Fluticasone 50micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free
201. Fluticasone 50micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
202. Fluticasone 50micrograms/dose inhaler CFC free
203. Fluticasone furoate 184micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler
204. Fluticasone furoate 92micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler
205. Fluticasone propionate 100microgram inhalation powder blisters
206. Fluticasone propionate 100microgram inhalation powder blisters with device
207. Fluticasone propionate 100micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler
208. Fluticasone propionate 100micrograms/dose dry powder inhaler
209. Fluticasone propionate 250microgram inhalation powder blisters
210. Fluticasone propionate 250microgram inhalation powder blisters with device
211. Fluticasone propionate 250micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler
212. Fluticasone propionate 250micrograms/dose dry powder inhaler
213. Fluticasone propionate 500microgram inhalation powder blisters
214. Fluticasone propionate 500microgram inhalation powder blisters with device
215. Fluticasone propionate 500micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler
216. Fluticasone propionate 500micrograms/dose dry powder inhaler
217. Fluticasone propionate 50microgram inhalation powder blisters
218. Fluticasone propionate 50microgram inhalation powder blisters with device
219. Fluticasone propionate 50micrograms/dose dry powder inhaler
220. Fluticasone Propionate Accuhaler 100 micrograms/dose
221. Fluticasone Propionate Accuhaler 250 micrograms/dose
222. Fluticasone Propionate Accuhaler 500 micrograms/dose
223. Fluticasone Propionate Disks with diskhaler 50 micrograms/dose
224. Fluticasone Propionate Disks with diskhaler 500 micrograms/puff
225. Fluticasone Propionate Inhaler 125 micrograms/puff
226. Fluticasone Propionate Inhaler 250 micrograms/puff
227. Fluticasone Propionate Inhaler 50 micrograms/puff
228. Flutiform 125micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)
229. Flutiform 250micrograms/dose / 10micrograms/dose inhaler (Napp Pharmaceuticals Ltd)
230. Flutiform 50micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)
231. Flutiform K-haler 125micrograms/dose / 5micrograms/dose breath actuated inhaler (Napp Pharmaceuticals Ltd)

232. Flutiform K-haler 50micrograms/dose / 5micrograms/dose breath actuated inhaler (Napp Pharmaceuticals Ltd)
233. Fobumix Easyhaler 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
234. Fobumix Easyhaler 320micrograms/dose / 9micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
235. Fobumix Easyhaler 80micrograms/dose / 4.5micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
236. Foradil 12microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
237. Formoterol 12microgram inhalation powder capsules with device
238. Formoterol 12micrograms/dose dry powder inhaler
239. Formoterol 12micrograms/dose inhaler CFC free
240. Formoterol 6micrograms/dose dry powder inhaler
241. Formoterol Dry Powder Inhaler 12 micrograms/actuation, 120 dose
242. Formoterol Dry Powder Inhaler 12 micrograms/actuation, 60 dose
243. Formoterol Easyhaler 12micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
244. Fostair 100micrograms/dose / 6micrograms/dose inhaler (Chiesi Ltd)
245. Fostair 200micrograms/dose / 6micrograms/dose inhaler (Chiesi Ltd)
246. Fostair NEXThaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (Chiesi Ltd)
247. Fostair NEXThaler 200micrograms/dose / 6micrograms/dose dry powder inhaler (Chiesi Ltd)
248. Franol Plus tablets (Sanofi)
249. Franol tablets (Sanofi)
250. Fusacomb Easyhaler 50micrograms/dose / 250micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
251. Fusacomb Easyhaler 50micrograms/dose / 500micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
252. Indacaterol 125micrograms/dose / Mometasone 127.5micrograms/dose inhalation powder capsules with device
253. Intal 20mg Spincaps (Sanofi)
254. Intal 20mg/2ml nebuliser solution unit dose vials (Aventis Pharma)
255. Intal 5mg/dose Fisonair with spacer (Sanofi)
256. Intal 5mg/dose inhaler (Aventis Pharma)
257. Intal 5mg/dose inhaler CFC free (Sanofi)
258. Intal 5mg/dose Syncroner with spacer (Aventis Pharma)
259. Intal Autohaler 5 mg/metered dose
260. Intal Compound Spincaps
261. Kelhale 100micrograms/dose inhaler (Cipla EU Ltd)
262. Kelhale 50micrograms/dose inhaler (Cipla EU Ltd)
263. Ketotifen 1mg capsules
264. Ketotifen 1mg tablets
265. Ketotifen 1mg/5ml oral solution sugar free
266. Ketotifen 1mg/5ml oral solution sugar free (Imported)

267. Ketotifen 1mg/5ml oral solution sugar free (Special Order)
268. Montelukast 10mg tablets
269. Montelukast 4mg chewable tablets sugar free
270. Montelukast 4mg granules sachets sugar free
271. Montelukast 5mg chewable tablets sugar free
272. Nedocromil 2mg/dose inhaler
273. Nedocromil 2mg/dose inhaler CFC free
274. Nedocromil 2mg/dose inhaler with spacer
275. Neovent 25micrograms/dose inhaler CFC free (Kent Pharma (UK) Ltd)
276. Norphyllin SR 225mg tablets (Teva UK Ltd)
277. Novolizer Budesonide Inhalation Cartridge + Device 200 micrograms/dose, 100 doses
278. Novolizer Budesonide Inhalation Cartridge Refill 200 micrograms/dose, 100 doses
279. Nucala 100mg powder for solution for injection vials (GlaxoSmithKline UK Ltd)
280. Nucala 100mg/1ml solution for injection pre-filled pens (GlaxoSmithKline UK Ltd)
281. Nuelin 125mg tablets (3M Health Care Ltd)
282. Nuelin 60mg/5ml liquid (3M Health Care Ltd)
283. Nuelin SA 175mg tablets (Mylan)
284. Nuelin SA 250 tablets (Mylan)
285. Omalizumab 150mg powder and solvent for solution for injection vials
286. Omalizumab 150mg/1ml solution for injection pre-filled syringes
287. Omalizumab 75mg/0.5ml solution for injection pre-filled syringes
288. Oxis 12 Turbohaler (AstraZeneca UK Ltd)
289. Oxis 6 Turbohaler (AstraZeneca UK Ltd)
290. Phyllocontin Continus 225mg tablets (Napp Pharmaceuticals Ltd)
291. Phyllocontin Forte Continus 350mg tablets (Napp Pharmaceuticals Ltd)
292. Phyllocontin Paediatric Continus 100mg tablets (Napp Pharmaceuticals Ltd)
293. Prednisolone 1mg tablets
294. Prednisolone 2.5mg tablets
295. Pro-Vent Capsules 300 mg
296. Pulmicort 0.5mg Respules (AstraZeneca UK Ltd)
297. Pulmicort 100 Turbohaler (AstraZeneca UK Ltd)
298. Pulmicort 100micrograms/dose inhaler CFC free (AstraZeneca UK Ltd)
299. Pulmicort 1mg Respules (AstraZeneca UK Ltd)
300. Pulmicort 200 Turbohaler (AstraZeneca UK Ltd)
301. Pulmicort 200micrograms/dose inhaler (AstraZeneca UK Ltd)
302. Pulmicort 200micrograms/dose inhaler CFC free (AstraZeneca UK Ltd)
303. Pulmicort 200micrograms/dose inhaler with Nebuchamber (AstraZeneca UK Ltd)
304. Pulmicort 400 Turbohaler (AstraZeneca UK Ltd)
305. Pulmicort LS 50micrograms/dose inhaler (AstraZeneca UK Ltd)
306. Pulmicort Ls Refill canister 50 micrograms/dose
307. Pulmicort Refill canister 200 micrograms/dose

308. Pulmicort Spacer inhaler 200 micrograms/dose
309. Pulmicort Spacer inhaler 50 micrograms/dose
310. Pulmicort Turbohaler Breath-Actuated Dry Powder Inhaler 100 micrograms/dose
311. Pulmicort Turbohaler Breath-Actuated Dry Powder Inhaler 200 micrograms/dose
312. Pulmicort Turbohaler Breath-Actuated Dry Powder Inhaler 400 micrograms/dose
313. Pulvinal Beclometasone Dipropionate 100micrograms/dose dry powder inhaler (Chiesi Ltd)
314. Pulvinal Beclometasone Dipropionate 200micrograms/dose dry powder inhaler (Chiesi Ltd)
315. Pulvinal Beclometasone Dipropionate 400micrograms/dose dry powder inhaler (Chiesi Ltd)
316. Qvar 100 Autohaler (Teva UK Ltd)
317. Qvar 100 inhaler (Teva UK Ltd)
318. Qvar 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
319. Qvar 50 Autohaler (Teva UK Ltd)
320. Qvar 50 inhaler (Teva UK Ltd)
321. Qvar 50micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
322. Relvar Ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)
323. Relvar Ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)
324. Salmeterol 25micrograms/dose inhaler
325. Salmeterol 25micrograms/dose inhaler CFC free
326. Salmeterol 50microgram inhalation powder blisters
327. Salmeterol 50microgram inhalation powder blisters with device
328. Salmeterol 50micrograms/dose dry powder inhaler
329. Salmeterol Xinafoate Disks with diskhaler 50 micrograms/blister
330. Seebri Breezhaler 44microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
331. Sereflo 25micrograms/dose / 125micrograms/dose inhaler (Cipla EU Ltd)
332. Sereflo 25micrograms/dose / 250micrograms/dose inhaler (Cipla EU Ltd)
333. Seretide 100 Accuhaler (GlaxoSmithKline UK Ltd)
334. Seretide 125 Evohaler (GlaxoSmithKline UK Ltd)
335. Seretide 250 Accuhaler (GlaxoSmithKline UK Ltd)
336. Seretide 250 Evohaler (GlaxoSmithKline UK Ltd)
337. Seretide 50 Evohaler (GlaxoSmithKline UK Ltd)
338. Seretide 500 Accuhaler (GlaxoSmithKline UK Ltd)
339. Serevent 25micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
340. Serevent 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
341. Serevent 50microgram disks (GlaxoSmithKline UK Ltd)
342. Serevent 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
343. Serevent 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
344. Singulair 10mg tablets (Organon Pharma (UK) Ltd)
345. Singulair Paediatric 4mg chewable tablets (Organon Pharma (UK) Ltd)

346. Singulair Paediatric 4mg granules sachets (Organon Pharma (UK) Ltd)
347. Singulair Paediatric 5mg chewable tablets (Organon Pharma (UK) Ltd)
348. Sirdupla 25micrograms/dose / 125micrograms/dose inhaler (Mylan)
349. Sirdupla 25micrograms/dose / 250micrograms/dose inhaler (Mylan)
350. Slo-Phyllin 125mg capsules (Merck Serono Ltd)
351. Slo-Phyllin 250mg capsules (Merck Serono Ltd)
352. Slo-Phyllin 60mg capsules (Merck Serono Ltd)
353. Sodium cromoglicate 20mg inhalation powder capsules
354. Sodium cromoglicate 20mg/2ml nebuliser liquid unit dose vials
355. Sodium cromoglicate 5mg/dose breath actuated inhaler
356. Sodium cromoglicate 5mg/dose inhaler
357. Sodium cromoglicate 5mg/dose inhaler CFC free
358. Sodium cromoglicate 5mg/dose inhaler with spacer
359. Sodium Cromoglicate Inhaler With Integral Spacer Device 5 mg/actuation
360. Soltel 25micrograms/dose inhaler CFC free (Cipla EU Ltd)
361. Soprobec 100micrograms/dose inhaler (Glenmark Pharmaceuticals Europe Ltd)
362. Soprobec 200micrograms/dose inhaler (Glenmark Pharmaceuticals Europe Ltd)
363. Soprobec 250micrograms/dose inhaler (Glenmark Pharmaceuticals Europe Ltd)
364. Soprobec 50micrograms/dose inhaler (Glenmark Pharmaceuticals Europe Ltd)
365. Spiriva Respimat 2.5micrograms/dose inhalation solution cartridge with device (Boehringer Ingelheim Ltd)
366. Spiriva Respimat 2.5micrograms/dose inhalation solution refill cartridge (Boehringer Ingelheim Ltd)
367. Stalpex 50micrograms/dose / 500micrograms/dose dry powder inhaler (Glenmark Pharmaceuticals Europe Ltd)
368. Symbicort 100/6 Turbohaler (AstraZeneca UK Ltd)
369. Symbicort 100micrograms/dose / 3micrograms/dose pressurised inhaler (AstraZeneca UK Ltd)
370. Symbicort 200/6 Turbohaler (AstraZeneca UK Ltd)
371. Symbicort 200micrograms/dose / 6micrograms/dose pressurised inhaler (AstraZeneca UK Ltd)
372. Symbicort 400/12 Turbohaler (AstraZeneca UK Ltd)
373. Tedral Tablets
374. Theo-Dur 200mg tablets (AstraZeneca UK Ltd)
375. Theo-Dur 300mg tablets (AstraZeneca UK Ltd)
376. Theograd Tablets 350 mg
377. Theophylline 125mg modified-release capsules
378. Theophylline 125mg tablets
379. Theophylline 175mg modified-release tablets
380. Theophylline 200mg modified-release tablets
381. Theophylline 250mg modified-release capsules
382. Theophylline 250mg modified-release tablets

383. Theophylline 300mg modified-release tablets
384. Theophylline 400mg modified-release tablets
385. Theophylline 50mg/5ml oral solution
386. Theophylline 50mg/5ml oral suspension
387. Theophylline 60mg modified-release capsules
388. Theophylline 60mg/5ml oral solution
389. Theophylline Capsules 300 mg
390. Theophylline Hydrate Syrup 125 mg/5 ml
391. Theophylline Paediatric tablets 200 mg
392. Theophylline S/R Capsules 300 mg
393. Theophylline S/R Tablets 500 mg
394. Theophylline Tablets 120 mg
395. Theophylline Tablets 200 mg
396. Theophylline Tablets 250 mg
397. Theophylline Tablets 300 mg
398. Theophylline Tablets 350 mg
399. Theophylline Tablets 400 mg
400. Tilade 2mg/dose inhaler (Sanofi)
401. Tilade 2mg/dose inhaler CFC free (Sanofi)
402. Tilade 2mg/dose Syncroner with spacer (Sanofi)
403. Tiotropium bromide 2.5micrograms/dose / Olodaterol 2.5micrograms/dose inhalation solution cartridge CFC free
404. Tiotropium bromide 2.5micrograms/dose inhalation solution cartridge CFC free
405. Tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device CFC free
406. Ultibro Breezhaler 85microgram/43microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
407. Uniphyllin Continus 200mg tablets (Napp Pharmaceuticals Ltd)
408. Uniphyllin Continus 300mg tablets (Napp Pharmaceuticals Ltd)
409. Uniphyllin Continus 400mg tablets (Napp Pharmaceuticals Ltd)
410. Ventide inhaler (GlaxoSmithKline UK Ltd)
411. Ventide Paediatric Rotacaps (GlaxoSmithKline UK Ltd)
412. Ventide Rotacaps (GlaxoSmithKline UK Ltd)
413. Ventide Rotahaler (GlaxoSmithKline UK Ltd)
414. Vertine 25micrograms/dose inhaler CFC free (Teva UK Ltd)
415. Xolair 150mg powder and solvent for solution for injection vials (Novartis Pharmaceuticals UK Ltd)
416. Xolair 150mg/1ml solution for injection pre-filled syringes (Novartis Pharmaceuticals UK Ltd)
417. Xolair 75mg/0.5ml solution for injection pre-filled syringes (Novartis Pharmaceuticals UK Ltd)
418. Zaditen 1mg capsules (Novartis Pharmaceuticals UK Ltd)

419. Zaditen 1mg tablets (CD Pharma Srl)
420. Zaditen 1mg/5ml elixir (CD Pharma Srl)
421. Zafirlukast 20mg tablets

Appendix H: (A) consultation type and (B) staff job categories for medical contact allocation

(A) Table of consultation types

#	consmedcodeid	**Term**	**true_consultation**
1	1572871000006117	Awaiting clinical code migration to EMIS Web	FALSE
2	1672871000006114	GP Surgery	TRUE
3	62151000000116	Telephone consultation	TRUE
4	62251000000110	Scanned document	FALSE
5	87821000000119	Externally entered note	FALSE
6	87941000000117	Administration note	FALSE
7	1807271000006114	Inbound document	FALSE
8	62141000000119	Telephone call to a patient	TRUE
9	1772691000000111	Outbound referral	FALSE
10	1672891000006110	Telephone call to relative/carer	TRUE
11	1672851000006116	Face to face consultation	TRUE
12	1778991000006111	Consultation via SMS text message	FALSE
13	1958701000006114	Online communication	TRUE
14	1780456010	Telephone triage encounter	TRUE
15	1780459015	E-mail received from patient	FALSE
16	62211000000111	Clinic note	FALSE
17	1948811000006117	Enterprise consultation	FALSE
18	63431000000112	Third party consultation	FALSE
19	90461000000113	Other note	FALSE
20	1672901000006114	Telephone call from relative/carer	TRUE
21	600851000000117	Consultation via video conference	TRUE
22	63381000000118	Telephone call from a patient	TRUE
23	294671000000119	Non-consultation data	FALSE
24	1672911000006112	Discussion with colleague	FALSE
25	1809171000006114	Routine consultation	TRUE
26	63371000000115	Hospital outpatient report	FALSE
27	600831000000112	Consultation via multimedia	FALSE
28	1773301000006111	E-mail consultation	FALSE
29	1672621000006114	Walk-in clinic	TRUE
30	482291000000111	SMS text message sent to patient	FALSE
31	285327012	Telephone encounter	TRUE
32	63341000000114	Home visit note	TRUE
33	1780460013	E-mail sent to patient	FALSE
34	282730013	Medication requested	TRUE
35	480941000000110	Nurse telephone triage	TRUE

36	1809181000006112	Emergency consultation	TRUE
37	1779001000006111	Other consultation medium used	FALSE
38	1809161000006119	Urgent consultation	TRUE
39	1672881000006112	Face to face consultation with relative/carer	TRUE
40	285368015	Emergency appointment	TRUE
41	63421000000110	Mail from patient	FALSE
42	63471000000114	OOH report	FALSE
43	173141000006118	Repeat prescription	TRUE
44	62181000000110	Laboratory result	FALSE
45	301141000000112	Seen in GP unit	TRUE
46	62131000000111	Hospital inpatient report	FALSE
47	1672921000006116	Case conference	FALSE
48	1672861000006119	Group consultation	FALSE
49	62191000000112	Mail to patient	FALSE
50	2219601000000111	School visit note	FALSE
51	661591000000118	Email received from carer	FALSE
52	1931821000006119	Same day appointment	TRUE
53	62241000000112	Nursing home visit note	FALSE
54	1809191000006110	Extended hours consultation	TRUE
55	1879181000006116	Discussion with other professional	FALSE
56	496351000000111	Provision of general practitioner intermediate care	TRUE
57	584851000000115	Seen in urgent care centre	TRUE
58	62101000000117	Residential home visit note	FALSE
59	1912201000006110	Multidisciplinary team meeting without patient	FALSE
60	294641000000113	Non-consultation medication data	FALSE
61	63441000000115	Children's home visit note	FALSE
62	8105161000006116	Remote consultation	TRUE
63	1778971000006110	Consultation via telemedicine web camera	TRUE
64	1969931000006119	Seen in influenza vaccination clinic	TRUE
65	1480626017	Telephone follow-up	TRUE
66	1772611000000119	Inbound referral	FALSE
67	1849991000006116	First telephone consultation	TRUE
68	63451000000117	Night visit note	TRUE
69	87781000000110	Twilight visit note	TRUE

(B) Table of staff job categories

#	Description	unscheduled_visit	Notes
1	Health Care Support Worker	FALSE	Scheduled
2	General Medical Practitioner	TRUE	Unscheduled
3	Receptionist		NA
4	Clerical Worker		NA
5	Sessional GP	TRUE	Unscheduled
6	Community Practitioner	TRUE	Unscheduled
7	Consultant	FALSE	Scheduled
8	Pharmacist	FALSE	Scheduled
9	GP Registrar	TRUE	Unscheduled
10	Community Nurse	FALSE	Scheduled
11	Manager		NA
12	System Administrator		NA
13	Medical Student		NA
14	Locum GP	TRUE	Unscheduled
15	Healthcare Assistant	FALSE	Scheduled
16	Senior Administrator		NA
17	Specialist Nurse Practitioner	FALSE	Scheduled
18	Midwife		NA
19	Salaried General Practitioner	TRUE	Unscheduled
20	Community Administrator		NA
21	Staff Nurse	FALSE	Scheduled
22	Medical Secretary		NA
23	Desktop Support Administrator		NA
24	Associate Practitioner - General Practitioner	TRUE	Unscheduled
25	Other Community Health Service - Admin Clerk		NA
26	Physiotherapist	FALSE	Scheduled
27	Associate Practitioner - Nurse	FALSE	Scheduled
28	Secretary		NA
29	Phlebotomist	FALSE	Scheduled
30	Dispenser	FALSE	Scheduled
31	Counsellor	FALSE	Scheduled
32	Nurse Consultant	FALSE	Scheduled
33	Appointments Clerk		NA
34	Medical Technical Officer - Pharmacy		NA
35	Analyst		NA
36	Senior Manager		NA
37	Technician - Admin & Clerical		NA

38	Paramedic	TRUE	Unscheduled
39	Dietitian		NA
40	Paramedic Specialist Practitioner	TRUE	Unscheduled
41	Associate Specialist	FALSE	Scheduled
42	Community Mental Health Nurse	FALSE	Scheduled
43	Clinical Coder		NA
44	Sister/Charge Nurse	FALSE	Scheduled
45	Enrolled Nurse	FALSE	Scheduled
46	Nurse Manager	FALSE	Scheduled
47	Other Community Health Service		NA
48	Chiropodist/Podiatrist	FALSE	Scheduled
49	Practitioner	FALSE	Scheduled
50	System Worker		NA
51	Physician Assistant	TRUE	Unscheduled
52	Clinical Assistant	FALSE	Scheduled
53	Information Officer		NA
54	Physiotherapist Specialist Practitioner	FALSE	Scheduled
55	Advanced Practitioner	TRUE	Unscheduled
56	Desktop Support Technician		NA
57	Helper/Assistant		NA
58	Helpdesk Administrator		NA
59	Health Records Administrator		NA
60	Specialist Practitioner	FALSE	Scheduled
61	Clinical Psychologist	FALSE	Scheduled
62	Trainee Practitioner	FALSE	Scheduled
63	Modern Matron	FALSE	Scheduled
64	Medical Records Clerk		NA
65	Student Practice Nurse	FALSE	Scheduled
66	Social Care Support Worker	FALSE	Scheduled
67	Other Community Health Service - Social Care Worker	FALSE	Scheduled
68	Clinical Application Administrator		NA
69	Associate Practitioner	TRUE	Unscheduled
70	Assistant Practitioner	TRUE	Unscheduled
71	Call Operator		NA
72	Researcher		NA
73	House Officer - Post Registration	TRUE	Unscheduled
74	Assistant GP	TRUE	Unscheduled
75	Availability Monitor		NA
76	Health Records Clerk		NA
77	Audit Manager		NA

78	Physiotherapist Consultant	FALSE	Scheduled
79	Therapist	FALSE	Scheduled
80	Psychotherapist	FALSE	Scheduled
81	Social Worker	FALSE	Scheduled
82	Student Nurse - Adult Branch	FALSE	Scheduled
83	Occupational Therapist	FALSE	Scheduled
84	Pre-reg Pharmacist	FALSE	Scheduled
85	Midwife - Sister/Charge Nurse	FALSE	Scheduled
86	Officer		NA
87	Medical Technical Officer		NA
88	Senior House Officer	TRUE	Unscheduled
89	Gateway Worker		NA
90	Dietitian Specialist Practitioner		NA
91	Clinical Team Manager		NA
92	Nursery Nurse		NA
93	Student Community Practitioner	FALSE	Scheduled
94	Community Worker (children)	FALSE	Scheduled
95	Psychiatrist	FALSE	Scheduled
96	Helpdesk Technician		NA
97	Network Administrator		NA
98	Paramedic Consultant	TRUE	unscheduled
99	Medical Records Manager		NA
100	Deputising Doctor	TRUE	Unscheduled
101	Student Health Visitor		NA
102	Osteopath	FALSE	Scheduled
103	Audiologist	FALSE	Scheduled
104	Dietitian Consultant	FALSE	Scheduled
105	Community Team Manager		NA
106	Midwife - Specialist Practitioner	FALSE	Scheduled
107	Radiographer	FALSE	Scheduled
108	Student Technician	FALSE	Scheduled
109	Student District Nurse	FALSE	Scheduled
110	Health Visitor	FALSE	Scheduled
111	Technician - Additional Clinical Services	FALSE	Scheduled
112	Network Technician		NA
113	Multi Therapist		NA
114	Patient Welfare Officer		NA
115	Technician - Healthcare Scientists		NA
116	Trust Grade Doctor - SHO level	TRUE	Unscheduled
117	Hospital Practitioner	TRUE	Unscheduled
118	Midwife - Consultant	FALSE	Scheduled
119	Physiotherapist Manager	FALSE	Scheduled
120	Directory of Services Coordinator		NA
121	Midwife - Manager		NA
122	Social work assistant (mental health)	FALSE	Scheduled
123	Chiropodist/Podiatrist Consultant	FALSE	Scheduled

124	Mental Health Act Administrator	FALSE	Scheduled
125	Asst. Clinical Medical Officer	FALSE	Scheduled
126	Clinical Medical Officer	FALSE	Scheduled
127	Student Physiotherapist	FALSE	Scheduled
128	Community Learning Disabilities Nurse	FALSE	Scheduled
129	Healthcare Cadet		NA
130	House Officer - Pre Registration	TRUE	Unscheduled
131	Staff Grade	TRUE	Unscheduled
132	Senior Clinical Medical Officer	TRUE	Unscheduled
133	Multi Therapist Specialist Practitioner	FALSE	Scheduled
134	Dietitian Manager		NA
135	Finance Director		NA
136	Biomedical Scientist		NA
137	Senior social worker (mental health)	FALSE	Scheduled
138	Waiting List Clerk		NA
139	Chiropodist/Podiatrist Specialist Practitioner	FALSE	Scheduled
140	Trainer		NA
141	Optometrist	FALSE	Scheduled
142	unscheduled	TRUE	Unscheduled
143	Assistant Psychologist	FALSE	Scheduled
144	Specialist Registrar	TRUE	Unscheduled
145	Occupational Therapy Specialist Practitioner	FALSE	Scheduled
146	Porter		NA
147	Healthcare Scientist		NA
148	Support, Time, Recovery Worker	FALSE	Scheduled
149	Approved Social Worker	FALSE	Scheduled
150	Clinical Director - Medical	TRUE	Unscheduled
151	Chiropodist/Podiatrist Manager	FALSE	Scheduled
152	Radiologist	FALSE	Scheduled
153	Social services care manager (adults)	FALSE	Scheduled
154	Healthcare Science Associate		NA
155	Intermediate Care staff	FALSE	Scheduled
156	Clinical Director		NA
157	Interpreter		NA
158	Radiographer - Diagnostic, Specialist Practitioner	FALSE	Scheduled
159	Ward Manager		NA
160	Chaplain		NA
161	Childcare Co-ordinator		NA
162	Speech & Language Therapist	FALSE	Scheduled
163	Radiographer - Diagnostic	FALSE	Scheduled
164	Trust Grade Doctor - Career Grade level	TRUE	Unscheduled
165	Board Level Director		NA
166	Child Protection worker	FALSE	Scheduled
167	Social services care manager (mental health)		NA
168	Waiting List Manager		NA
169	Radiographer - Therapeutic, Manager	FALSE	Scheduled

170	Ward Clerk		NA
171	Trust Grade Doctor - Specialist Registrar level	TRUE	Unscheduled
172	Art Therapist		NA
173	Healthcare Science Assistant	FALSE	Scheduled
174	Social work assistant (adults)	FALSE	Scheduled
175	Occupational Therapist Consultant	FALSE	Scheduled
176	Complaints Investigator		NA
177	Radiographer - Diagnostic, Manager	FALSE	Scheduled
178	Senior social worker (adults)	FALSE	Scheduled
179	Student Psychotherapist	FALSE	Scheduled
180	Medical Director		NA
181	Nursery manager		NA
182	Art Therapist Manager		NA
183	ODP		NA
184	Technician - PS&T		NA
185	Art Therapist Specialist Practitioner		NA
186	Art Therapist Consultant		NA
187	Student Midwife	FALSE	Scheduled
188	Other Executive Director		NA
189	Home Care organiser		NA
190	Caldicott Guardian		NA
191	Specialist Healthcare Science Practitioner		NA
192	Chief Executive		NA
193	Nursing Cadet		NA
194	Student Community Mental Health Nurse	FALSE	Scheduled
195	Trust Grade Doctor - House Officer level	TRUE	Unscheduled
196	Intermediate Care worker	FALSE	Scheduled
197	Occupational Therapist Manager	FALSE	Scheduled
198	Social services senior management	FALSE	Scheduled
199	Social work team manager (mental health)		NA
200	Director of Public Health		NA
201	Orthoptist	FALSE	Scheduled
202	Student Orthoptist	FALSE	Scheduled
203	Outpatient Manager		NA
204	Student Occupational Health Nurse	FALSE	Scheduled
205	Chair		NA
206	Social work team manager (adults)		NA
207	Student Dietitian	FALSE	Scheduled
208	Student School Nurse	FALSE	Scheduled
209	Home help		NA
210	Art, Music & Drama Student		NA
211	Social Services information manager		NA
212	Director of Nursing		NA
213	Medical Laboratory Assistant		NA
214	Orthoptist Manager		NA
215	Trainee Scientist		NA

216	Non Executive Director		NA
217	SODP		NA
218	Consultant Healthcare Scientist		NA
219	Reporting Radiographer	FALSE	Scheduled
220	Special salary scale in Public Health Medicine		NA
221	Dental Assistant Clinical Director		NA
222	Regional Dental Officer		NA
223	Student Occupational Therapist		NA
224	Professor		NA
225	General Dental Practitioner	FALSE	Scheduled
226	Specialist Healthcare Scientist		NA
227	Student Nurse - Mental Health Branch	FALSE	Scheduled
228	Healthcare Science Practitioner	FALSE	Scheduled
229	Assistant Psychotherapist	FALSE	Scheduled
230	Playgroup leader		NA
231	Student Nurse - Learning Disabilities Branch	FALSE	Scheduled
232	OT assistant	FALSE	Scheduled

Appendix I: TRAINS Data Processing

TRAINS: Data Processing Document

Version 1.0, 2021-11-01, Ric Campbell

Data sources

A list of data sources that were used during the project.

Table 1: Data sources used in the TRAINS project

Dataset Name	Inclusion Criteria	Exclusion Criteria	Date Range
Clinical Practice Research Datalink (CPRD)	**GPs** General Practices (GPs) who are currently part of the CPRD in England, and where randomised in the study (list provided) **Children** School aged children with asthma aged between 4 to 16 years old as of 1st September 2021 with a coded diagnosis of asthma (diagnosis list provided), who have been prescribed asthma medication in the last 12 months (medicines list provided).	**GPs** GPs not included in CPRD or cease to be part of it during the invention time without contributing to the primary outcome. GPs not in England. **Children** Children under 4 and over 16 years old as of 1st September 2021. Children with no asthma diagnosis. Children with asthma who have not received a prescription for asthma medication in the last 12 months (lists provided).	GP practice last contribution date: 2020-02-10 to 2022-03-21

Table 2. Record numbers per data source used in the TRAINS project

Dataset Name	**Metric**	*Number*
Clinical Practice Research Datalink (CPRD)	Distinct patient identifiers (patid), none removed.	105,994

Clinical Practice Research Datalink (CPRD) data

CPRD identified and extracted all eligible records from its information systems. Patients in the data had to be:

- Aged between 4 to 16 years old as of 2021-09-01, born between 2005-09-01 and 2017-08-31 (inclusive)
- Registered at a practice that was randomised by CPRD for the TRAINS study, these are listed in 'TRAINS randomisation for CRPD.txt'
- Only GP practices in England
- Patients must have a recorded diagnosis of asthma. Relevant asthma diagnoses are listed in 'Asthma diagnosis codes 4 April.txt'
- Patients must have an asthma drug prescription in the past 12 months (2020-06-01 to 2021-05-31, inclusive), indicating active asthma. Relevant asthma drugs are listed in 'Asthma related drug treatment codes 8 April.txt'
- Patients must be alive at the end point of the primary analysis period (2021-07-31).

No identifiable data was provided in the dataset.

Processing activities

Practices

Duplicated Practice

One practice ID (20155) was found to be duplicated in the randomisation file. This was due to the practice size deciles being created from National practice codes and then being converted into CPRD practice codes. CPRD were unable to fix this, and could not say which data was true for this practice. This practice was removed from the data and not included in any analysis datasets.

Practice Merges

There are three ways that practices can merge in relation to the study:

1) Only the source practice (the practice that stops "existing") contributes to CPRD.
   For these, this is the same as a practice leaving CPRD Aurum, so treatment depends on the last data that was provided. If this is in the relevant time period practice data can be used.
2) Only the target practice (practice that continues "existing" gaining patients from a source practice) contributes to CPRD.
   The target practice 'original' patients are unaffected. The new patients will increase the practice size (that we do not have access to), but their historic data

will be available. This has to happen before the intervention to ensure that all patients have the same exposure.

3) Both practices contribute to CPRD Aurum.
   This is fine if both practices are in the same arm, but this is something we do not know. If this occurs between baseline and intervention, all data should be available and no difference has occurred.
   If practices merge during intervention then patients could be in different arms and we would not be aware.
   Practices that are still contributing data cannot be a source practice, but they could be a target practice.

For scenario 2), there are no dates where multiple people joined a practice on the same day, that might indicate a practice merge (or patients are registered at their first contact).

Breakdown of practices:

There were 1,491 practices in the May 2022 Aurum build.
Reduced to 1,389 keeping only those in the randomisation file
Reduced to 1,387 removing one duplicate, and one that was no longer in Aurum database
Reduced to 1,386 when limiting the data to only children in the timeframe of interest.
Reduced to 1,385 when limiting the data to only children with a diagnosis of interest.
Reduced to 1,359 when limiting the data to only children who have been prescribed an asthma medication in the past 12 months (2020-06-01 to 2021-05-31).

Of the data received from CPRD that included these 1,359 practices, one practice id had been duplicated and was removed from the data as it was not possible to distinguish which records were correct. Leaving **1,358** practices

However, practices may have left/merged and would still be present in the data, but they would have just stopped providing new data to Aurum database.

Last Contribution Date

There was 1 practice whose last contribution date was **before** the start date of interest (2020-06-01), included due to a single prescription after the last contribution date (this could be due to repeat prescription in advance or data entry error).

There was 32 practices whose last contribution was **after** the start date of interest, but **before** the end date of interest (2021-12-31)

A field was created indicating when the last contribution date fell;

- Pre the period of interest (before August 2021)
- After the first month of the primary outcome (afterAugust 2021)
- After the second month of the primary outcome (after September 2021)

- After months included in some secondary outcomes (after October/ after November/ after December 2021)

Patients

Acceptable Patients

All patients who have been flagged by CPRD as not being acceptable for research purposes have been removed from the dataset. CPRD checks a patient's data for non-continuous follow up or patients with poor data recording. If any of the following condition are true, the patient is flagged as unacceptable for research:

- Year of birth is empty
- Current registration date is empty
- Current registration date is greater than the practice's last collection date
- Current registration date is less than or equal to 01/01/1900
- Current registration date is equal to or greater than the registration end date
- Current registration date is prior to the birth year
- Gender other than male, female or indeterminate
- Age is greater than 115 at end of follow-up (based on registration end date, death or last collection date)
- All recorded health care episodes have empty event dates
- All recorded health care episodes have invalid events dates (less than or equal to 01/01/1900 or greater than last collection date)
- All recorded health care episodes have dates before the birth year
- Patients are not permanently registered

Age

CPRD deletes the month of birth when a person turns 16 (although how this is done has not been made clear). From the data that we received in April 2022, most patients who were born in either 2005 or 2006 have no month of birth, despite those born in May 2006 onwards would still be 15 and therefore *should* have a month of birth.

As school years stretch across years it means for those without a month of birth we know that that:

Year of birth: 2005. Patient could be in either:
- Year 12 (born January - August), and would not be viable for inclusion, or
- Year 11 (born September - December), and would be viable for inclusion.

Year of birth: 2006. Patient could be in either:
- Year 11 (born January - August), and would be viable for inclusion, or
- Year 10 (born September - December), and would be viable for inclusion.

From this it was decided that:

- all patients with a year of birth of 2005 (and no month of birth?) would be excluded from the study.
- All patients with a year of birth of 2006 (and no month of birth?) would be considered 15-16, therefore making an analysis of school years not possible past year 9.

Age calculation

There are ages calculated from two dates of interest for the study:

1. The school year a patient was in, and therefore the age on 2021-09-01
2. The age at the end of the primary outcome, 2021-09-31.

1. If a patient was born at any point in September (1st - 31st), they will be in the same school year. For this we can set the 'birth date' to September 1st for the age calculation.
2. If a patient was born at any point in September (1st - 31st), they will be the same age at the end of September. For this we can set 'birth date' to September 1st for the age calculation.

So, despite there being two ages of interest calculated at different dates, only one calculation is needed.

For patients with a birth year of 2006 and no birth month, a 'date of birth' was created of 2006-01-01, making all age calculations equal 15 for these patients.

Ethnicity

A codelist from opencodelists.org, a depository for code lists created by the OpenSAFELY team, was downloaded that linked SNOMED codes and readable terms.

A mapping list form NHS Digital gitHub repository was also saved, linking SNOMED codes to 2021 census grouping categories.

These lists were merged giving a more complete list of SNOMED codes related to a patient's ethnicity. As the two lists differed, some codes did not have a readable term, while others did not have a census grouping, this would be added manually later once only those used in the data were identified. (Census grouping was confirmed by the project team).

This list was then linked to the CPRD medical dictionary by SNOMED code, giving paired terms and medcodes which are used in the Observations table of CPRD Aurum.

The Observation tables were then searched for all instances of medcodes that were present in this reference data. These records were used, along with the mapping data, as arguments for the AurumPipeline function add_ethnicity. This created a patient ethnicity look-up table, with a

patient's ID, readable ethnicity term, and census category grouping in one table, which was saved and used to add ethnicity information when needed.

Gender

The gender of all patients was limited to either Male or Female, with any others being set to NA (> 0.005%).

Asthma Diagnosis

From the data that was supplied by CPRD it was checked that for every patient that was present in the data, that they also had an asthma diagnosis in the observation table data that was provided. It was found that all patients did have at least one diagnosis from the list of asthma diagnosis codes selected to define the project definition of asthma.

Asthma Prescriptions

From the data that was supplied by CPRD it was checked that for every patient that was present in the data, that they had an asthma prescription in the drug table data within the past 12 months (2020-06-01 - 2021-05-31 inclusive) in the data provided. It was found that all patients did have at least one asthma drug prescription from the list of asthma drug codes selected as relevant asthma medications for the study.

Registration and De-registration

A field was created to indicate when a patient's registration date, the date they registered at their current practice, was before the start of the primary outcome period (August 2021).

A field was created to indicate at what time period they deregistered from their practice, which could represent either a transfer out (potentially to a new practice who does not contribute data to CPRD) or a death date. The groupings used were;

- Pre the period of interest (before August 2021)
- After the first month of the primary outcome (after August 2021)
- After the second month of the primary outcome (after September 2021)
- After months included in some secondary outcomes (after October/ after November/ after December 2021).

Drug Prescriptions

Records in the drugs table have two dates associated with them, the issuedate, the date which the drug is issued, and the enterdate, the date the event was entered into the EMIS Web system.

Issue Date

For almost all of the relevant asthma preventer records in the drug table, the issue date is before the last contribution date (lcd) of the practice (99.9%). However, there are some records which have a issuedate after the last contribution date, but for all these the enterdate was before the last contribution date.

A field was created to indicate if a drug prescriptions issue date was after the related practices last contribution date.

A field was created to indicate if a drug prescriptions issue date was after a patient's deregistration date.

Consultations

All consultation in the time frame of interest were taken and fields indicating if they were 'true medical contacts', and if they were scheduled or unscheduled visits were added.

'True medical contacts' were based on the consultation code, see the consultation_reason_codes_terms spreadsheet.

If a consultation was scheduled or unscheduled was based on the staff type that was associated with the consultation, see the job_category_descriptions spreadsheet.

There were consultation codes in the consultation table that were not in the medical dictionary, these were set to be counted as not true consultations, as were those consultations that did not have a consultation code.

All consultations were ordered by patient, date, and if it was a true medical contact and if it was unscheduled or scheduled.

Only one consultation was selected for each patient-date combination, with precedent taken for if it was a true medical contact and if it was an unscheduled consultation.

According to the protocol a scheduled contact is any contact that is part of the planned care for the patient, for example an asthma review; a medical review; repeat prescription or immunisation.

An unscheduled contact is any unplanned contact that is either patient initiated or as a result of illness.

Assumptions:

One ‘consultation’ (based on the combination of patient id, practice id and consultation id) in the consultation table is considered one contact.

All consultations data supplied are taken into account for the study not just those that are asthma related.

Where there are duplicate consultations (i.e. same patient id, consultation id and consultation type) the ‘duplicates’ are ignored.

Assumptions used to code records as scheduled or unscheduled (contact type) are based on clinical, immunisation, therapy, referral, test and consultation data.

Appendix J: Ethical approval for TRAINS study, including the university of Sheffield & ISAC for CPRD

1. The University of Sheffield ethics approval

The University Of Sheffield.

Downloaded: 26/04/2021
Approved: 26/04/2021

Rami Alyami
Registration number: 190258496
School of Health and Related Research
Programme: PhD/ScharrFTPLEASANTTrial ntvn

Dear Rami

PROJECT TITLE: TRial to Assess Implementation of New research in a primary care Setting (TRAINS): a pragmatic cluster randomised controlled trial
APPLICATION: Reference Number 037412

On behalf of the University ethics reviewers who reviewed your project, I am pleased to inform you that on 26/04/2021 the above-named project was **approved** on ethics grounds, on the basis that you will adhere to the following documentation that you submitted for ethics review:

- University research ethics application form 037412 (form submission date: 19/04/2021); (expected project end date: 14/11/2023).

If during the course of the project you need to deviate significantly from the above-approved documentation please inform me since written approval will be required.

Your responsibilities in delivering this research project are set out at the end of this letter.

Yours sincerely

Jennifer Burr
Ethics Administrator
School of Health and Related Research

Please note the following responsibilities of the researcher in delivering the research project:

- The project must abide by the University's Research Ethics Policy: https://www.sheffield.ac.uk/rs/ethicsandintegrity/ethicspolicy/approval-procedure
- The project must abide by the University's Good Research & Innovation Practices Policy: https://www.sheffield.ac.uk/polopoly_fs/1.671066!/file/GRIPPolicy.pdf
- The researcher must inform their supervisor (in the case of a student) or Ethics Administrator (in the case of a member of staff) of any significant changes to the project or the approved documentation.
- The researcher must comply with the requirements of the law and relevant guidelines relating to security and confidentiality of personal data.
- The researcher is responsible for effectively managing the data collected both during and after the end of the project in line with best practice, and any relevant legislative, regulatory or contractual requirements.

2. ISAC Approval

University of Sheffield

Rami AH Alyami <rahalyami1@sheffield.ac.uk>

Review of study TRial to Assess Implementation of New research in a primary care Setting (TRAINS): a pragmatic cluster randomised controlled trial of an educational intervention to promote prescription uptake in General Practitioner Practices is now complete
1 message

Clinical Practice Research Datalink <noreply-erap@cprd.com> 17 June 2021 at 10:52
To: RAHAlyami1@sheffield.ac.uk

Dear Mr Rami Alyami,

Your study 21_000436 – "TRial to Assess Implementation of New research in a primary care Setting (TRAINS): a pragmatic cluster randomised controlled trial of an educational intervention to promote prescription uptake in General Practitioner Practices " has been approved by CPRD. You can view any feedback by logging on to eRAP at https://www.erap.cprd.com/.

If your study requests access via a Study-specific dataset agreement and/or for CPRD to extract the study dataset, CPRD will get in touch with you to agree on the licence agreement and data specification.

If your study will access CPRD data via an Institutional multi-study licence and requests access to linked data (except NCRAS data), please complete the Linkage Request Form available for download at https://www.erap.cprd.com/, and return this to enquiries@cprd.com as soon as possible. Please also provide us with your patient identifiers (in the form of a tab delimited text file) and/or code lists to facilitate the provision of linked data. Once the data extraction team has reviewed your request, you will receive an acknowledgement email with a 10 working-day turn around for data delivery. Please note provision of NCRAS linked data follows a different process, as stated in the documentation and discussed prior to submission. CPRD will get in touch with you to agree on the licence agreement and data specification.

Should you require any advice regarding the implementation of your approved study please don't hesitate to contact us at enquiries@cprd.com.

Kind Regards,
CPRD

NIHR | National Institute for Health and Care Research